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SARCOMA OF THE BREAST

A Report of Twenty-two Cases

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BOSTON AND GREENFIELD, MASSACHUSETTS

RECENT studies show that sarcoma constitutes between 2 and 3 per cent of all malignant tumors of the breast, but since the medical literature of the past eighty years records less than 600 cases,[1] it seems that the diagnosis is often missed.

The combined records of the Pondville Hospital (Massachusetts Department of Public Health) and Massachusetts General Hospital back to 1923 contain 22 cases of breast sarcoma with reliable pathological diagnoses and follow-up notes. All 22 patients were women between the ages of eighteen and sixty-nine, and the average age was forty-four years. Comparable figures in a group of 60 patients treated at the Johns Hopkins Hospital from 1894 to 1934 give forty-nine years as an average age, with a range of thirteen to seventy-five years[2]; there were 2 male patients.

Classification

The terminology resulting from different pathological classifications is confusing to the surgeon. A practical and comparatively simple classification is suggested by Fox,[2] who divides all breast sarcomas into four groups as follows:

Group I. Fibrosarcoma
- (*a*) Fascial type (spindle-cell sarcoma, periductal angiosarcoma and fibrosarcoma)
- (*b*) Secondary to adenofibroma (adenofibrosarcoma)
- (*c*) Secondary to intracanalicular fibromyxoma (periductal myxosarcoma,[3] fibromyxosarcoma and cystosarcoma)

Group II. Neurogenic sarcoma (perineural fibrosarcoma and melanotic sarcoma)

Group III. Lymphoid and myeloid sarcoma (round-cell sarcoma)

Group IV. Miscellaneous nonindigenous sarcomas (giant-cell sarcoma, carcinosarcoma, angiosarcoma, liposarcoma and so forth)

Group I (fibrosarcoma) is by far the largest, containing 82 per cent of our cases and 70 per cent of those at the Johns Hopkins Hospital. The individual tumors in this group vary somewhat in degree of malignancy, but their clinical behavior is fairly constant and comparatively favorable. They tend to form large bulky tumors, to grow into contiguous structures by direct extension, not to metastasize to regional lymph nodes and not to invade the blood stream until late, if at all.

The other groups are less important because they include so few cases. The neurogenic sarcomas and the lymphoid and myeloid sarcomas are characterized by a high degree of malignancy and a fatal outcome. There are rapid growth, early metastasis to regional lymph nodes (especially in the lymphoid and myeloid types), early blood-stream invasion and early remote metastasis. The last group contains miscellaneous rare tumors whose behavior shows no group characteristics.

In Table 1, our 22 cases are compared with those reported by Fox. Approximately one third of the patients in both series are known to be dead of sarcoma, the two mortality rates being strikingly similar. The rate of curability is less accurate, since it is based on an arbitrary time limit of five years. On this basis, the curability for our series of 22 patients is not lower than 36 per cent, and that for the 18 patients in Group I (fibrosarcoma) is not lower than 44 per cent. A scrutiny of our 6 indeterminate cases shows that at least 3 are likely to be cured; this will raise the curability figures to 50 and 60 per cent, respectively. It is recognized that our figures are too small for the derivation of significant percentages.

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All 4 of our patients outside Group I died of sarcoma. To what extent this mortality rate should be ascribed to inadequate treatment and how accurately it reflects the fatal nature of the disease itself cannot be determined. It will be noted that the Johns Hopkins series also shows no five-year cures outside Group I.

TABLE 1. *Tabulation of Cases.*

TYPE	STATUS OF PATIENT	OUR CASES	FOX'S CASES
Group I (fibrosarcoma)	Dead of sarcoma	4 (22%)	10 (24%)
	Living and well at 5 years	8 (44%)	14 (33%)
	Living and well under 5 years	6	18
Totals		18	42
Group II (neurogenic sarcoma)	Dead of sarcoma	0	3
	Living and well at 5 years	0	0
	Living and well under 5 years	0	4
Totals		0	7
Group III (lymphoid and myeloid sarcomas)	Dead of sarcoma	1	5
	Living and well at 5 years	0	0
	Living and well under 5 years	0	2
Totals		1	7
Group IV (miscellaneous sarcomas)	Dead of sarcoma	3	1
	Living and well at 5 years	0	0
	Living and well under 5 years	0	3
Totals		3	4
All groups	Dead of sarcoma	8 (50%*)	19 (58%*)
	Living and well at 5 years	8 (50%*)	14 (42%*)
	Living and well under 5 years	6	27
Grand totals		22	60

*These percentages take no account of the cases followed for less than 5 years.

The treatment of these 4 cases happened to be inadequate. Two patients had local excision of small tumors, one of which proved to be a lymphoid sarcoma, and the other, a carcinosarcoma. The former refused further surgery and, after temporary improvement with x-ray treatment, died of multiple generalized metastases within six months. The latter died of metastases to the ribs, lungs and brain twenty months after a fruitless radical mastectomy undertaken after an unexplained delay of ten months. Both the remaining 2 patients had large angiosarcomas, one with known lung metastases. Palliative simple mastectomy was done for both. One died in two years of generalized metastases, and the other in six months of metastases to the lymph nodes and lungs. Thus, no conclusions concerning the possible effectiveness of ideal treatment can be drawn from these 4 cases.

A consideration of the treatment of the 18 cases in Group I (fibrosarcoma) is more instructive. Of 2 patients who had local excision of small tumors, one is alive after sixteen years, and the other, although she has survived operation for only four and a half years, is probably cured since no tumor tissue could be found when a wide excision of the scar was done ten months after the original operation.

Of the 11 patients treated by simple mastectomy, the 4 whose tumors were small (under 7 cm.) are alive — 2 for over five years and 2 for over two years. A fifth patient with a tumor of unrecorded size had simple mastectomy followed in two years by local recurrence in the form of a tumor 26 cm. in diameter. This was radically excised, and the patient is living and well three and a half years later (five and a half years after simple mastectomy). Of the remaining 6 patients, whose tumors were large (10 to 30 cm.), 3 are living after ten, five and a half, and two years, respectively. The other 3 died, 1 in two years of extension to pleura, 1 in two years of bone metastases, and 1 in six months of pulmonary metastases.

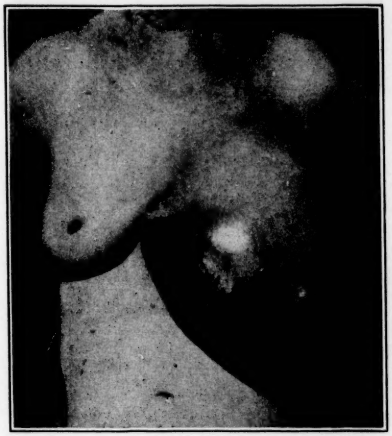

FIGURE 1.

This sixty-four-year-old patient had had painless swelling of the breast for nine months. The pathologist reported "adenofibrosarcoma." The patient was living and well five years and three months after simple mastectomy.

Radical mastectomy was undertaken as a primary procedure in only 4 cases. The 2 patients

whose tumors were small are alive and well after nine and seven years, respectively. Of the 2 patients whose tumors were large, one is alive for four years; the other was subjected to radical

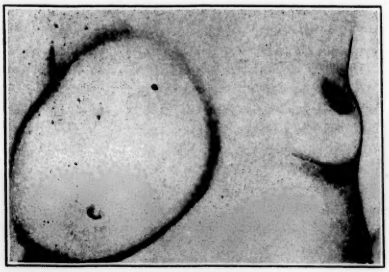

FIGURE 2.

This thirty-three-year-old patient had had painless swelling of the breast for about seven years. The pathologist reported "fibrosarcoma of breast and benign hyperplasia of lymph node." The patient was living and well two years after simple mastectomy, with lymph-node biopsy.

mastectomy on the chance that a suspicious area of bone destruction in the jaw might prove to be unrelated to her disease, but she died six months later with metastases to the jaw and scapula. It is

FIGURE 3.

This sixty-year-old patient had had a simple mastectomy for painless swelling of six months' duration, associated with trauma to the breast. The pathologist reported "adenofibrosarcoma." Nine months later, a radical operation was done for local recurrence, and the photograph shows a second recurrence twenty months after the last operation.

significant that the axillary lymph nodes were not affected in all 4 cases.

Finally, 1 patient whose operation is not well enough described to be classified lived ten and a half years and died of other causes.

Treatment

In an evaluation of the results of treatment in these 22 cases, the most striking conclusion is as follows: for patients in Groups II (neurogenic), III (lymphoid and myeloid) and IV (miscellaneous), the only hope of cure lies in radical mastectomy and axillary dissection before bloodstream and lymphatic invasion has occurred.

It appears equally clear that this is not true of patients in Group I (fibrosarcoma). There is

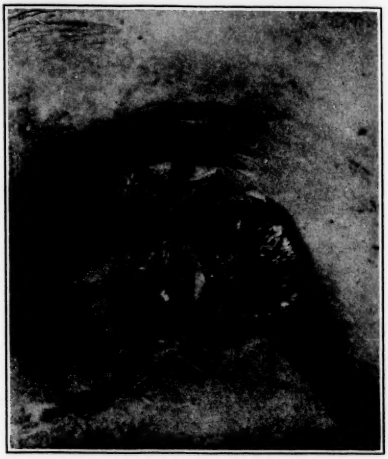

FIGURE 4.

This photograph of the patient in Figure 3 was taken eight months after a block excision of the chest wall, including three ribs and a portion of the pleura. There is a third local recurrence. The patient died four months later from extension of the tumor into the pleural and peritoneal cavities.

evidence that axillary dissection is not necessary in this group. In none of our 18 cases were lymph-node metastases demonstrated, whereas unaffected lymph nodes were found in 9 cases. Furthermore, 6 patients whose axillary nodes were not removed are still alive. On the other hand, it seems unwise to rely on either local excision or simple mastectomy for cure. Since death from tumors of the fibrosarcoma group is due to extension of the tumor into fascia or blood vessels, at least the pectoral fascia and preferably the pectoralis muscle should be removed, as well as the breast. This procedure, which would have added little to the risk of simple mastectomy, would probably have prevented 2 of our 3 deaths and obviated a massive local recurrence in another case.

Undoubtedly the reason so-called "palliative simple mastectomy" is so often done for enormous tumors of the breast is that the surgeon is thinking in the more familiar terms of carcinoma, and it does not occur to him that so large a tumor could possibly be curable. Six of our Group I (fibrosarcoma) patients presented this picture and received this treatment, some with the preoperative diagnosis of "advanced cancer of the breast." Three are apparently cured, in spite of an inadequate operation. There is good reason to think that 5 of the 6 might have been cured if a curative rather than a palliative operation had been done.

Diagnosis

The diagnosis of breast sarcoma depends on microscopic examination. Even for the pathologist, it is not always easy to recognize the different types of malignant tumor or even to tell whether a tumor is malignant or benign. All that the surgeon can do is keep in mind the possibility of sarcoma and remember that not all large tumors are incurable. A large tumor, particularly in the absence of palpable axillary nodes, is probably either a comedo carcinoma, benign tumor or fibrosarcoma. Neither the patient's age nor a story of trauma has any diagnostic value. The story of a small tumor that after having been the same size for several years suddenly begins to grow larger is suggestive of fibrosarcoma, but is not diagnostic. The presence of cystic areas, bluish discoloration of the skin and conspicuous dilated veins over a large, lobulated tumor is almost pathognomonic of sarcoma.

Prognosis

In 8 fatal cases, the average duration of life after operation was seventeen months, the shortest three months, and the longest forty-one months. The average time from onset of symptoms to death was twenty-seven months, the shortest six months, and the longest forty-seven months.

No definite correlation can be found between prognosis and age, nor does the duration of symptoms furnish any reliable aid. The type of tumor appears to be of the greatest significance, tumors of the fibrosarcoma group offering the best prognosis; Group III (lymphoid and myeloid sarcoma) tumors offer the worst, and tumors of the other groups are in between.

The size of the tumor appears to have prognostic significance only in Group I (fibrosarcoma). With tumors less than 5 cm. in diameter, the ratio of dead to living patients was 0:5; between 5 and 10 cm., it was 1:3; and between 10 and 30 cm., it was 3:8.

Summary and Conclusions

Twenty-two cases of breast sarcoma are reported, with a discussion of their classification, treatment and results.

Of 18 patients (82 per cent) whose tumors were classed as fibrosarcomas, 8 (44 per cent) are known to be cured for at least five years, 6 are living under five years, and 4 are known to be dead of sarcoma. Of 4 patients whose tumors were classed as lymphoid sarcoma, angiosarcoma or carcinosarcoma, all are known to be dead of sarcoma.

The treatment of choice for tumors of the fibrosarcoma type is surgical removal of the breast and pectoralis major muscle, without dissection of the axilla. If the tumor is small and has not invaded the blood stream, the prognosis is excellent.

The only possibility of cure for the other types of sarcoma is by early radical mastectomy with axillary dissection. Regardless of the size and short duration of the tumor, the prognosis is poor unless the tumor is a fibrosarcoma.

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PNEUMONIA: A STUDY OF ONE HUNDRED AND THIRTY-TWO CASES TREATED IN THE HOME WITH SULFATHIAZOLE*

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BOSTON

DURING the winter of 1940–41, 132 patients with pneumonia were treated in their homes by the Domiciliary Medical Service of the Boston Dispensary. This free service by the Boston Dispensary was established in 1796 for care of the indigent sick in their homes. In a discussion of this service, Wing[1] states:

> The burden of home care of the sick who are unable to employ a physician is usually a responsibility of the local rather than of the state or federal government. It is commonly exercised as a function of the Public Welfare or Poor authorities rather than of medical institutions. . . . Boston, unlike other cities of the country, has never employed city physicians for this purpose but has accepted the services of privately supported medical charity as a substitute.

The physicians on this service have two or more years of postgraduate hospital work and are appointed as fellows in medicine for one year. They spend their mornings in the Out-Patient Department, and their afternoons, in making home visits. Their work is supervised by a full-time physician who also acts in the capacity of consultant. Approximately 50,000 visits are made annually.

During the winter months, many cases of pneumonia are seen, and in the past, because of inadequate home facilities for the treatment of pneumonia then available, it was necessary to hospitalize most of these patients. This, no doubt, threw an additional burden on the already overcrowded hospitals in Boston. With the introduction of the sulfonamides, it seemed reasonable to believe that many of these patients could be successfully treated in their own homes. This led to the formation of the Pneumonia Service, consisting of four district physicians particularly interested in this work. These men were made available during and after their regular hours to study and treat patients in whom a diagnosis of pneumonia was made. Two physicians were designated to care for adults, and two for infants and children.

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METHODS

All cases of pneumonia or suspected pneumonia seen by the district physicians were referred through the district office to the physician on the Pneumonia Service, who visited the patient within a few hours. If the diagnosis of pneumonia was confirmed, the following course was instituted: the history was taken, and physical examination was made for corroboration of the diagnosis; sputum was obtained for typing, nose or throat swabs being taken in children; leukocyte and erythrocyte counts, and hemoglobin estimations were made, and blood films for differential counts were taken; a blood culture was obtained; and a urinalysis was made.‖

Following this, the treatment was begun at once. The drug chosen was sulfathiazole, because of its effectiveness and slight degree of toxicity.[2–12] It was assumed that patients were likelier to follow the treatment carefully if such distressing symptoms as nausea and vomiting were eliminated. In most cases, an amount of sulfathiazole sufficient for twenty-four hours was supplied by the physician, and the first dose was usually administered in his presence.

The dosage in pneumonia in adults was 4 gm. (60 gr.) as an initial dose, followed by 1 gm. every four hours, day and night, until the patient's temperature had been normal for seventy-two hours, although in some cases this was reduced to 1 gm. every six hours during the afebrile stage, after which the drug was discontinued. In children, the initial dose was 0.065 gm. (1 gr.) per pound of body weight. Following this, a daily dosage of 0.065 gm. per pound was administered daily, divided into six equal parts given every four hours, day and night, until the temperature had been normal for thirty-six hours, when the drug was discontinued.

Fluids were forced during the administration of the drug. Patients were instructed to take 3000 cc. (3 quarts) of fluid daily. The output was followed. If the urine fell below 1500 cc. in twenty-four hours, the cause was investigated, and additional fluid given. Recommended fluids consisted of stimulants, such as coffee, tea and Coca-Cola, fluids high in carbohydrate, such as fruit

‖Sputums and blood cultures were examined in the Bacteriological Laboratory of the Massachusetts Department of Public Health.

juices, and mineral-containing liquids, such as broth, soup and bouillon made from cubes (each cube containing 2 or 3 gm. of salt). In children, a simple mixture of 3 tablespoonfuls of carbohydrate (sugar, Karo and so forth) and 1 teaspoonful of salt in 500 cc. (1 pint) of water was used to give approximately 5 per cent glucose and saline.

The patients were followed daily until complete recovery. If residual chest signs persisted, the patient was referred to the Out-Patient Department for a roentgenogram of the chest. After careful consideration, it was decided not to determine the blood sulfathiazole levels, and our experience shows that it was not necessary.

Supportive treatment consisted mainly of high-calorie diets, sedation for chest pain, general nursing care and, not the least important, the tender ministrations of the patient's own family. The assistance rendered to the patients and the district service by the Community Health nurse in this respect cannot be too highly praised. No oxygen, digitalis or artificial stimulants were used during the course of home treatment.

Results

Age

The ages ranged between two months and eighty-six years. Approximately half the patients were below the age of twelve; 23, or approximately 17 per cent of the entire group, were above the age of fifty. Three patients were between eighty and ninety years of age.

Sex

Seventy-four (56 per cent) of the entire group were males, and 58 (44 per cent) were females.

Duration of Illness before Treatment

In pneumonia, the value of early treatment needs no comment. Because in most cases the patients were seen early, the treatment could be instituted as soon as the physician on the Pneumonia Service had confirmed the diagnosis of the attending physician. Table 1 shows that in the majority of cases the treatment was instituted within forty-eight hours after the onset of the illness; 9 patients were treated within twelve hours of the onset. Such factors as objection to hospitalization, family consultation, arrangements for care of children, waiting for ambulances and the necessary delay in examination and admission to the hospital are eliminated by home treatment.

Table 1. *Duration of Illness before Treatment.*

Days	No. of Cases
½ or less	9
1	46
2	30
3	22
4	13
5	4
6	3
7	4
8	1
Total	132

Typing of Sputum

Pneumococci were found in the sputum of 70 cases (53 per cent) of the total of 132. In some patients who showed no pneumococci in the first sputum examination, a second sample was obtained, but this was positive in only 1 case. Table 2 shows the distribution of positive sputums by types. Sixty per cent of the patients with positive sputums were above the age of twelve years. In evaluating the clinical data, we compared the patients whose sputum showed pneumococci with those in whom none were found.

Table 2. *Types of Pneumococci Recovered.*

Type	No. of Cases
1	11
5	9
8	8
2	5
4	4
6	4
3	3
14	3
29	3
33	3
7	2
9	2
15	2
20	2
23	2
10	1
13	1
16	1
18	1
17	1
38	1
31	1
Total	70

Signs and Symptoms

In general, the signs and symptoms were similar in both groups of patients. The commonest presenting symptoms in the patients with pneumococci in the sputum were pain (67 per cent), dyspnea (63 per cent), frank chills (51 per cent) and bloody sputum (33 per cent). In all but the oldest age group, the clinical appearance presented was that of an extremely acute illness.

Temperature, Pulse and Respirations

The initial temperatures, pulses and respirations showed nothing remarkable and were characteristic of the disease in most cases.

Blood Cultures

An initial blood culture was obtained in every case but 1. Positive blood cultures were present in 6 cases. In a sixty-four-year-old patient, a Type

8 pneumococcus was found in the sputum, and blood culture was negative. Examination during a relapse a few days later showed a Type 8 pneumococcus in the sputum, and another blood culture was positive for Type 8 pneumococcus. In another case, a sixty-seven-year-old man (Case 10) first seen on the seventh day of his illness, had no pneumococci in the sputum, but a Type 2 pneumococcus was recovered from the blood culture. He expired on the day after treatment was started. In another case, there was a Type 5 pneumococcus in the sputum, and a similar type in the blood. One patient had a Type 1 pneumococcus in the sputum and blood. A twenty-two-month-old child, who showed no pneumococci in the sputum but had a positive blood culture, — Type 18, — made an uneventful recovery after three days; further treatment was refused by the family at the end of this time. Another patient, a five-year-old child, who showed no pneumococci in the sputum but Type 1 pneumococcus in the blood, made an uneventful recovery after three days of treatment. The mortality of the small group of cases with positive blood cultures was 17 per cent.

Blood Examinations

The initial white-cell counts ranged from 2000 to more than 50,000. A leukopenia was not considered a contraindication for sulfathiazole therapy.

Red-cell counts and hemoglobin determinations showed normal variations. After therapy in most cases, there was a definite drop in the white-cell count, but there was leukopenia in only 1 case. In this patient, the white-cell count fell to 3800 per cubic millimeter, with 44 per cent granulocytes after three days of treatment, but with continued therapy, the count rose to 10,700.

In Case 10, mentioned above, the initial white-cell count was 2000; a second count taken on the day after therapy was instituted showed a rise to 3400, although the patient died on that same day.

No marked drop in hemoglobin or red-cell count was noticed.

Urinalyses

Very few complications referable to the urinary tract were observed throughout the treatment. One outstanding feature was that in 40 patients the initial urinalyses showed the presence of albumin, white blood cells, red blood cells or casts or various combinations of them. This, in almost every case, cleared up rapidly under therapy with sulfathiazole. Twenty-four patients showed sulfathiazole crystals in the urinary sediment during treatment.

One patient showed gross hematuria. Sulfathiazole was stopped, and the urine became clear after about a week. A small group of patients showed microscopic blood, which cleared up after treatment was stopped. There were no cases of anuria, and although it was rather difficult to measure correctly the fluid intake and output, we can safely say that in none of these cases was there evidence of retention of fluid in the tissues.

Duration of Fever

An interesting factor to be considered is the interval between the institution of therapy and the drop in temperature to normal. The average length of time before the temperature dropped to normal was about forty-eight hours (Table 3).

TABLE 3. *Duration of Fever.*

DURATION *hours*	NO. OF CASES
CASES WITH PNEUMOCOCCI	
24 or less	23
36	3
48	21
60	1
72	7
Over 72	15
Total	70*
CASES WITHOUT PNEUMOCOCCI	
12 or less	2
24	37
36	0
48	17
60	1
72	4
Over 72	4
Unknown	1
Total	66*

*The additional 4 cases represent relapses.

Total Dosage of Sulfathiazole

Two groups of patients are considered: those who showed pneumococci in the sputum, and those who did not. Furthermore, adults and children are considered separately.

It was found that in the typed cases, adults received an average of 37 gm. of sulfathiazole, and children required an average of 12 gm. In the nontyped cases, adults received an average of 23 gm., and children an average of 10 gm.

Duration of Treatment

The average actual duration of treatment in the home seems to be less than that in patients treated at the hospital. It is quite possible that in many of these cases at home, as soon as the patients seemed to be well clinically, there was a tendency on the part of the family to stop all medication. This apparently had little effect on the ultimate outcome of the disease.

Since there was no direct control over the administration of the drug and since family co-operation was not always complete, the physician usually gave the initial large dose before leaving the patient. Platt[13] has suggested that a single large dose is frequently therapeutically effective, and in several cases, this proved to be so.

The average duration of treatment — not including fatal and hospitalized cases — was 4.0 days for the adults and 3.6 days for the children who had pneumococci in the sputum; among the patients who did not have pneumococci in the sputum, the average duration was 3.8 days for adults and 3.4 days for children.

Toxic Symptoms

The outstanding toxic symptom observed in these cases was vomiting, which was noted in 20 cases. It was quite evident that in some of these the vomiting was due to the disease rather than to the drug, since it also occurred before treatment. In no case did this symptom become a serious problem. Three patients had some abdominal distention, which might or might not have been due to the drug.

A papular rash on the face and trunk was observed in one case, and a nodular erythematous rash on the extremities in another. Gross hematuria occurred in 1 patient, and microscopic hematuria in a few, as mentioned above.

A rise of temperature that could definitely be attributed to sulfathiazole was not noted in any of the cases, possibly because of the short duration of treatment.

Complications

One patient developed, on the third day, a pleural friction rub over the involved portion of lung. It disappeared after four days. One patient stricken with pneumonia in her third month of pregnancy made an uneventful recovery. A twenty-eight-year-old man with a Type 3 pneumococcus in the sputum who was hospitalized because of poor home conditions developed an empyema at the hospital and was treated by thoracotomy. A thirty-five-year-old man with a Type 1 pneumococcus developed evidence of fluid in the chest after a week of treatment, and this was found to be due to a serous pleurisy. He was hospitalized, and chest taps showed no evidence of empyema. He was discharged on the ninth hospital day following an uneventful recovery.

Four infants had pertussis in addition to pneumonia. One patient developed diabetic acidosis and had to be hospitalized. Altogether, 11 patients in the entire group had to be hospitalized for various reasons.

Deaths

The 5 fatal cases seem worthy of individual comment.

Case 10. W. D. (B. D. D. 88711), a 67-year-old man, was treated for cirrhosis of the liver in August, 1940, at the Boston City Hospital. This patient, who was a chronic alcoholic, was seized with pain in the right chest on the evening of December 25, 1940, and then with fever and increase of cough. He had had a common cold for several days previously. He was first seen by a district physician on December 31. The temperature was 102.4°F., and the pulse 120. A mistaken diagnosis of influenza was made. On January 1, 1941, the temperature was 100.4°F., the respirations 40, and the pulse 140. Lobar pneumonia involved both lower lobes. The white-cell count was 2000. On prolonged examination of the smear, only 1 neutrophil, 9 lymphocytes and 2 monocytes were found. The urine contained a large trace of albumin, numerous casts and 1.4 per cent sugar. No pneumococci were found in the sputum. A Type 2 pneumococcus was grown from the blood. Sulfathiazole, begun on January 1, the 8th day of the illness, was discontinued after a day owing to the leukopenia and nephritis. This was a mistake, since the blood on January 2, after 9 gm. of sulfathiazole had been given, contained 3400 leukocytes, of which 18 per cent were neutrophils. The urine on January 2 was free from sugar. The patient died the following night.

Case 14. J. W. (B. D. D. 111921), a 41-year-old man, complained of fever, chilly sensations and aching pains in the extremities on December 26, 1940 — 5 days before treatment with sulfathiazole was begun. On the following day, there was a cough, with copious tenacious brownish sputum; the patient was a chronic alcoholic, and his landlady stated that he was probably drinking throughout the early part of his illness. The temperature was 102°F., the respirations 38, and the pulse 120. Pneumonia of the right middle and lower lobes was found. A Type 5 pneumococcus was found in the sputum and blood. Since the patient failed to improve, he was sent on January 3 to the Massachusetts Memorial Hospitals, where in addition to the sulfathiazole he was given 300,000 units of antipneumococcus (Type 5) serum after a blood culture on January 3 was found to be positive. He failed to gain and died on January 14, the 26th day of his illness.

Case 47. N. B. (B. D. D. 83850), an 83-year-old man, had been under treatment for chronic congestive failure of the heart for over 2 years when, on January 12, 1941, he was seized with a shaking chill lasting 2 hours and followed by fever. When seen on the following day, he had a cough and was raising yellow sputum. The temperature was 100°F., the respirations 32, and the pulse 92; the patient was dyspneic. Bronchopneumonia of both lower lobes was found. The white-cell count was 21,100. A Type 9 pneumococcus was found in the sputum. The blood culture was negative. Sulfathiazole treatment was begun. In 24 hours, the temperature fell to 98°F., the respirations to 24, and the pulse to 74. On the following day, the patient was greatly improved, and there was no dyspnea. The temperature was 98.2°F., and the pulse 78. The temperature was normal for 5 days — from January 14 to 19. Then, there was a recurrence of fever and pneumonia. The patient died on January 24, the 13th day of his illness.

Case 128. A. B. (B. D. D. 95716), a 79-year-old man, toward the end of March, 1941, was found to have cerebral thrombosis, with increased weakness of the left side of the body and toes. He also had chronic heart failure and senility. He had had hemiplegia a year previously. On April 5, cough, fever and labored breathings were noted. On April 9, the patient was semicomatose. He was first seen on April 10, when the temperature was 100°F., the respirations 40, and the pulse 80. Pneumonia of the right lower and left upper and lower lobes was found. Treatment with sulfathiazole was begun. The total amount

given during 6 days was 40 gm. No pneumococci were found in the sputum, and the blood culture was sterile. The patient did not respond to treatment and died on April 16, the 12th day of the disease.

CASE 153. M. M. (B. D. D. 119301), a 77-year-old woman, was seized with a shaking chill, followed by fever and cough, on January 21, 1941. The patient had had congestive heart failure during the previous year. She was first seen on January 23, when the temperature was 102°F., the respirations 32, and the pulse 100 — the rate at the apex being 120. Auricular fibrillation was present. Pneumonia involving both lower lobes was found. The heart was slightly enlarged on percussion. The liver edge was felt three fingerbreadths below the costal margin. There was no sputum, but a swab made from the pharynx yielded Type 5 pneumococci. The blood culture was negative. Treatment with sulfathiazole was begun on January 24. The patient was too weak to move in bed, and was incontinent and semicomatose; the eyes were sunken and glazed. She was sent to the Boston City Hospital, apparently moribund. She lived, however, until February 7, the 20th day of her illness. Autopsy revealed a lobar pneumonia, general arteriosclerosis, cardiosclerosis and chronic pulmonary tuberculosis involving both apexes.

Response of Children

The response of infants and children to treatment in the home was especially satisfactory. Most parents were very co-operative in following directions, and the supportive measures and general care were adequately administered. The absence of the psychic trauma of removal to unfamiliar surroundings was believed to be a positive factor in the success of home treatment. The absence of abdominal distention, except in 2 infants, suggests that the emotional strain attending hospitalization may be a causative element in the development of this complication. Convalescence appeared to be a more pleasant period, and hence more tolerable, when the patient was surrounded by familiar toys and faces. No difficult problems in child management peculiar to the treatment of pneumonia in the home arose.

SUMMARY AND CONCLUSIONS

One hundred and thirty-two cases of pneumonia were successfully treated in the home during the winter months under adverse conditions, as the total mortality (5 patients, or 3.8 per cent) indicates. Pneumococci in the sputum were obtained in 70 cases, and 6 patients had positive blood cultures. The mortality rate for cases with pneumococci in the sputum was 6 per cent. There were very few toxic manifestations due to the drug, and no cases of hemolytic anemia or granulopenia. Few urinary complications and no fever due to the drug were noted.

This work represents a financial saving to the community of several thousands of dollars that would have been incurred if these patients had been treated in hospitals.

The study indicates that pneumonia may be treated at home by the use of sulfonamides with death rates as low as or lower than those obtained in hospital practice, provided treatment is begun early in the disease.

During the winter season of 1941 and 1942, 85 additional cases of pneumonia were treated with sulfadiazine with only 1 death. That was in a seventy-five-year-old woman, who, during the course of treatment, developed marked abdominal distention, was hospitalized and died on the third hospital day; a post-mortem examination disclosed partial intestinal obstruction due to a carcinoma of the small bowel, with extensive metastases to the lungs and liver, and massive bilateral pneumonia.

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ELECTROENCEPHALOGRAPHIC STUDIES IN CHILDREN PRESENTING BEHAVIOR DISORDERS*

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BOSTON

IN CHILDREN and adolescents presenting behavior disorders, the relative consequence of environmental and biologic factors in the individual case should be determined, since the more capable one is of evaluating these factors in patients, the more intelligent the therapeutic approach will be.

Smith[1] has found that the development of the electrocortical activity of infants follows the course of the myelinating cerebrum. The electroencephalogram can therefore be used as a valuable measure of the structural and functional maturity of the brain.

Lindsley[2] and Smith[3] have shown that the adult pattern of the electrical brain potentials is not established until late childhood or early adolescence. They have demonstrated, and we have been able to confirm, from our own studies, that there are individual variations in the age in which the adult pattern is stabilized.

Jasper, Solomon and Bradley,[4] in their studies of childhood behavior disorders, noted that 71 per cent of the patients had abnormal electroencephalograms. Half the abnormal tracings were found in cases in which there was no other objective evidence of cerebral dysfunction. Strauss, Rahm and Barrera[5] observed abnormal electroencephalograms in 59 per cent of 22 children with primary behavior disorders. Lindsley and Cutts,[6] from their study of "constitutionally inferior" and behavior-problem children, found the electroencephalograms different from those of normal children in three ways: high alpha cycles, with 2 to 5 cycles per second; an increase in the number of 5 to 8 cycles per second; and vulnerability of the testing pattern to hyperventilation. These studies indicate that in a high percentage of behavior-problem children, one is dealing with an immature or abnormally functioning cerebrum. Hence, the electroencephalogram may afford an objective measure of the physical immaturity of the brain.

At the Boston Psychopathic Hospital, we have obtained tracings on 143 children presenting behavior disorders (106 boys and 37 girls). Sixty-eight were sent by the courts of Greater Boston for psychiatric study. Seventy-five were referred by physicians at the request of their parents; thirty-five of these children came from foster parents.

Of the 143 children, 125 had normal physical and neurologic findings and no history of an illness involving the central nervous system. Seven had histories of head injury followed by a period of unconsciousness; 6 had histories of chorea; 3 had a questionable history of encephalitis; and 2 may have had seizures prior to the age of seven. The average intelligence quotient of the group was 87, with a range from 65 to 134. Indication of a poorly integrated personality was brought out by the number who had a history of neurotic traits (enuresis, nail biting, and walking and talking in their sleep). Ninety had one or more neurotic traits, 32 had none, and in 21 no information was given.

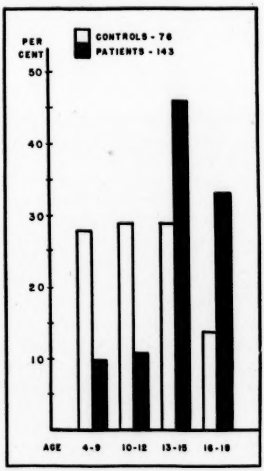

FIGURE 1. *Percentage Distribution of Controls and Patients in Age Groups.*

The influence of the child's position in the sibling group did not seem to play a very significant role, for just as many occupied an intermediate

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position as those who were the oldest, youngest or only child.

The family background revealed only 18 normal families. Of the 143 patients, 16 had psychotic parents, 4 had a family history of epilepsy, and 76 came from homes broken because of desertion, divorce or death of parents, 36 of the last being referred from foster homes. Parents of 43 were chronic alcoholics, parents of 43 were openly hostile, and those of 28 were oversolicitous. A striking fact is that only 17 patients had other siblings who were behavior problems.

The problems that led to admission were many. Forty-six were admitted for stealing, 33 for sexual misbehavior, 32 for being runaways and 21 for temper tantrums; 15 were called "stubborn children" by the courts, 13 were truants, 9 set fires and 5 were depressed. A number of children had more than one type of undesirable behavior.

All the children adjusted themselves well on the wards and gave no evidence of being behavior problems, except for 21 who were overactive, sullen, vindictive, noisy or destructive, or had temper tantrums when verbally reproached.

Since a study of juvenile delinquency by the Gluecks[7] stressed the fact that delinquency decreases with increase in maturity, it seemed advisable to divide the cases into age groups. The majority of patients were between the ages of thirteen and fifteen. This age range is a particularly vulnerable period, owing to the onset of puberty; therefore, our groups were built around this age range. Four groups were chosen: four to nine as the childhood period; ten to twelve as the preadolescent period; thirteen to fifteen as the early adolescent period; and sixteen to eighteen as the late adolescent period. Figure 1 shows the distribution of patients and controls.

Since we were dealing with an age range in which the normal electroencephalogram differs from the adult pattern and varies from year to year in its development into the adult pattern (Smith,[3] Lindsley[2] and Gibbs and Gibbs[8]), we obtained tracings on 76 control children (69 boys and 7 girls) of the same age range as the group of behavior-problem children. They were selected from a middle-class population, and to the best of our knowledge, they were from good homes and environment and were not recognized as presenting any problem at home, in school or in the community. Intelligence quotients were not available, but we estimate that the children were at least of average intelligence.

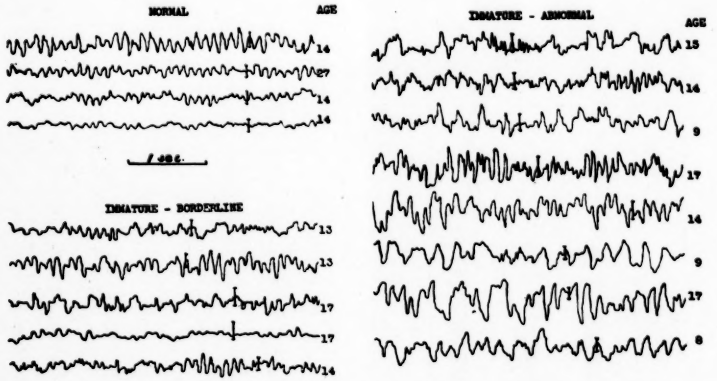

FIGURE 2. *Samples of Normal, Immature-Borderline and Immature-Abnormal Electroencephalographic Tracings.*

Most of the samples were taken from the older age groups. Some of the samples in the immature-borderline group, for example, the second one, would be considered normal in a child of six or seven. The vertical lines through the tracings represent 50 microvolts. It should be noted that the degree of amplification varies in the different tracings.

Apparatus and Procedure

The records were obtained with a Grass six-channel electroencephalographic apparatus. Electrodes were placed over the frontal, precentral and occipital regions of each hemisphere, the indifferent electrode being placed over the mastoid. Two types of records were obtained: six simultaneous recordings from each of the frontal, pre-

central and occipital areas of the two hemispheres, grounded to the indifferent mastoid electrode; and six simultaneous bipolar records, including the left frontal to left precentral, right frontal to right precentral, left precentral to right precentral, left precentral to left occipital, right precentral to right occipital, and left occipital to right occipital. The records were obtained with the patient lying down and with the eyes closed. Hyperventilation for a period of two minutes was done in all the controls and in most of the patients.

Analysis of Records

The tracings are divided into three groups: normal, immature-borderline and immature-abnormal (Fig. 2). Because of the normal immaturity of the pattern in childhood and early adolescence, it is impossible to say whether an atypical pattern at a given age represents a delay in the maturity of the pattern or whether it is secondary to some congenital or acquired injury to the brain. It would be incorrect to label a patient's brain waves as abnormal when the unusual activity might be due only to a delay in his maturity. Consequently, when patterns are not normal for a given age, we prefer to consider them either immature-borderline or immature-abnormal, depending on the degree to which they deviate from the normal pattern of that age range. The evaluation of hyperventilation in children is complicated by the fact that normally the brain potentials are more vulnerable to this procedure than those of adults. This vulnerability decreases with increase in age. We have used our controls as a guide in evaluating the response to hyperventilation in the patients.

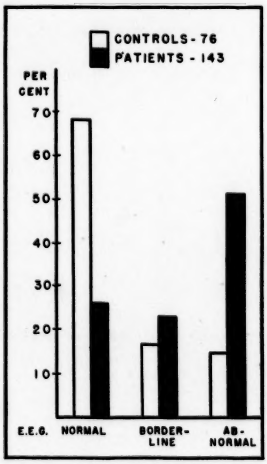

FIGURE 3. *Percentage Distribution of Normal, Immature-Borderline and Immature-Abnormal Electroencephalographic Tracings from Patients and Controls.*

Normal tracings are much less common in the behavior-disorder group.

Recently, Davis and Wallace[9] have demonstrated that brain potentials in normal persons who tend to run low blood-sugar levels or who have not eaten for several hours are vulnerable to hyperventilation. Since all our control records were obtained at five o'clock in the evening (four to five hours after lunch time), whereas most of the patients' records were obtained between one and two o'clock (one or two hours after lunch time), our controls were overweighted, so far as anomalies or hyperventilation, resulting from a low blood sugar, are concerned.

Results

Of 143 children presenting behavior disorders, 26 per cent had normal, 23 per cent borderline and 51 per cent abnormal electroencephalograms; whereas of the 76 controls, 68 had normal, 17 had borderline and 15 per cent abnormal tracings (Fig. 3). As a group, the electroencephalograms of the behavior disorders were more vulnerable to hyperventilation than those of the controls (Table 1). This finding is in agreement with the conclusions of Lindsley and Cutts.[6]

The controls and the patients were divided into age groups; and the percentages of normal, immature-borderline, and immature-abnormal records that occurred in each age group were compared. Moreover, when one compared age group with age group, there was, on the whole, a progressive increase in normal records and a diminution in abnormal records with increase in age (Fig. 4). There was no significant difference in the percentage of behavior-disorder children with abnormal records who were adjusted on the ward and those who continued to exhibit maladaptation.

TABLE 1. *Response of Electroencephalogram to Two Minutes of Hyperventilation.*

Type of Case	No Response	Moderate Response	Marked Response
	%	%	%
Controls (71 cases)	44	27	29
Behavior problems (42 cases)	23	33	44

Twenty-four (16 per cent) of the children with behavior disorders had inferior intelligence; and of these, 15 (62 per cent) had abnormal tracings. Of the 119 who had normal intelligence, 59 (50 per cent) had abnormal tracings. This is not a significant difference.

Discussion

This study demonstrates that the electrocerebral activity of many children with behavior disorders is not normal. A wave of slow rate is the commonest abnormal finding in these patterns. In the adult, such a wave is definitely abnormal, but in early childhood slow activity is a normal finding; therefore, a greater degree of slow activity than is consistent for a normal record of that age range may be due to a delay in the normal development of the cerebrum. A further evidence of immaturity in these cases was the frequent occurrence of neurotic traits, such as enuresis, thumb sucking and nail biting. The tracing is a measure of the delayed development of the cerebrum; because of this delay in development, these patients do not make a satisfactory adjustment either to their environment or to the impact of puberty — 46 per cent of the cases were between the ages of thirteen and fifteen. The fact that only 17 patients had siblings who were behavior problems, although subjected to the same environment, suggests that the environment is only a precipitating factor.

We believe that the electroencephalograph may become a useful adjunct in guiding therapeutic approach. For example, behavior-problem children with normal tracings might be expected to adjust themselves better with minor alterations in environmental stresses under proper psychiatric guidance. On the other hand, an abnormal tracing in such children indicates a degree of cerebral immaturity incommensurate with the chronological age reached, and therefore a child less likely to respond to minor variations in his milieu. An effort should immediately be made to place him in an environment modified to suit his limitations until he has achieved sufficient maturity.

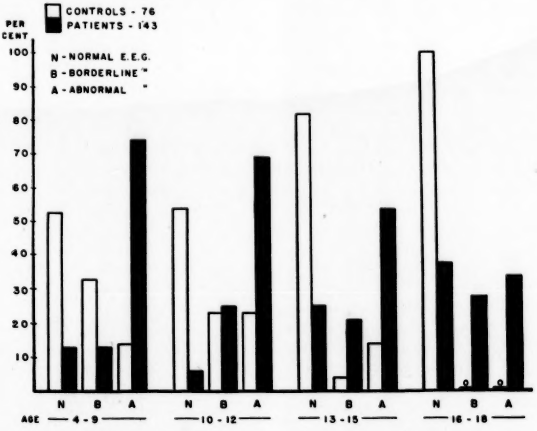

Figure 4. *Percentage Distribution of Normal, Immature-Borderline and Immature-Abnormal Electroencephalographic Tracings (Patients and Controls) in Each Age Group.*

There is a greater percentage of abnormal tracings in the behavior disorders in each group than in the controls. The diagram also illustrates that with increase in age there is a diminution in the percentage of immature-abnormal tracings in the children with behavior disorders.

Summary

The electroencephalograms of 143 children presenting behavior disorders are compared with those of a group of 76 normal controls of the same age range. The former had a higher percentage of immature-abnormal tracings and were more vulnerable to hyperventilation than the latter.

The patients and controls were divided into age groups: four to nine, ten to twelve, thirteen to fifteen and sixteen to eighteen. The patients with behavior disorders in each age group had a higher percentage of immature-abnormal tracings than the controls. Moreover, the records of the behavior disorders, comparing age group with age group, showed a progressive increase in normal records and a diminution in immature-abnormal records

with increase in age (from 74 per cent in the group from four to nine to 34 per cent in that from sixteen to eighteen). The possibility that the decrease in immature-abnormal records in the older age group was related to the maturation of the cerebrum is discussed.

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MEDICAL PROGRESS

ARTIFICIAL RADIOACTIVE ISOTOPES IN MEDICINE AND BIOLOGY*

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BOSTON

THE application of the isotopic tracer technic to medical investigation ranks in importance with the invention of the microscope and the discovery of the x-ray. During the relatively few years that isotopes have been employed in biologic research, they have contributed to fundamental discoveries in intermediary metabolism, and have provided new and promising forms of therapy for otherwise hopeless diseases.

The chief and unique value of isotopic tracers lies in their applicability to the study of normal metabolic processes in undisturbed organisms in functional, nutritional and energic equilibrium. Previous methods of metabolic study, which relied on chemical technics, were of necessity concerned with the determination of accumulations of unnatural intermediate or end products, and frequently utilized observations made on sick or deranged organisms. However, with the use of isotopic tracers, the ebb and flow and interchange of normal foodstuffs, intermediate metabolic products, vitamins and even hormones can be followed in intact, living organisms.

Briefly, isotopes are atoms with identical chemical and biologic properties (since their nuclear charges and atomic numbers are the same), and are distinguished only by differences in atomic weight. Some isotopes are stable, — that is, they never change, — whereas others are radioactive and sooner or later undergo nuclear changes with the emission of radiations (gamma rays, beta rays or alpha particles). The stable isotopes, because of the differences in their atomic weights, can be separated and detected quantitatively with the mass spectrometer, and the radioactive isotopes can be followed with an electroscope or a Geiger–Müller counter (instruments capable of detecting radiations). Since the organism does not distinguish between labeled and ordinary isotopes of the same element, biologic reactions in which the tracer isotope participates are identical with those occurring simultaneously with ordinary isotopes.[1–3] By the use of appropriate technics of detection, both stable and radioactive isotopes can therefore be employed in biologic research as marked or labeled atoms that serve to indicate the paths and reactions of their ordinary fellow atoms. It must be emphasized that the atoms of radioactive isotopes, except for slight differences in atomic weight, are indistinguishable from other atoms of the same element until they instantaneously give off their radiation. The amounts of radiation liberated by the minute "tracer doses" employed in biologic investigations are so small that they produce no alteration in normal physiologic processes, and it is only when large "therapeutic doses" are administered that radiation effects are produced.

The application of the isotopic tracer technic to biology is actually very simple. A substance — for example, an amino acid or a simple inorganic compound such as sodium phosphate — containing either stable or radioactive tracer atoms is fed to an animal or human subject, and subsequently the blood, tissues or secretions are tested for the presence of the labeled atoms. The presence of such atoms in any particular tissue indicates that some of the ingested material has been deposited in that tissue. In this fashion, the fate of the particular molecules of the amino acid or sodium phosphate

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. $4.00).

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that were fed to the experimental subject can be distinguished from the fate of similar but unlabeled molecules of amino acid or sodium phosphate already present in the body. For example, by injecting sodium bicarbonate labeled with radioactive carbon and subsequently demonstrating the presence of this radioactive carbon in glycogen from the liver, Conant and his associates[4] were able to show that the animal organism can utilize carbon dioxide for the synthesis of glycogen. This truly revolutionary discovery could have been accomplished only by the use of a technic that allowed distinction between carbon atoms in the injected sodium bicarbonate and the carbon atoms of the complex carbohydrates already present in the body.

As early as 1923, Hevesy,[5] using the naturally occurring radioactive isotope of lead (radium D), studied the circulation of lead in plants, and similar technics were later applied to bismuth. Naturally occurring radioactive isotopes are few in number, however, and therefore the radioactive tracer technic could not be extensively applied to biologic investigation. The discovery by Joliot and Curie[6] that atoms could be made radioactive by artificial means, and the invention and development of the cyclotron by Lawrence and Cooksey,[7] made possible the production of artificially radioactive isotopes of practically all the elements, and during the last six years, many of these radioactive substances have been employed in biologic investigation. As medical investigators become familiar with the possibilities of this technic, and as more strongly radioactive substances are prepared and the methods of detection are made more sensitive, the use of isotopic tracers will undoubtedly be greatly expanded and will allow approach to many problems hitherto impossible of solution.

Although the only essential difference between the stable and radioactive isotopic tracer technics lies in the method of detection, this report is limited to a discussion of the radioactive tracers. An excellent review of the biologic applications of the stable isotopes has recently been prepared by Schoenheimer and Rittenberg.[8]

The extensive applications of radioactive tracers to studies of plant[9] and insect[10] physiology are beyond the scope of this paper, which is intended primarily to summarize only the more significant contributions with direct bearing on medical science.

Complete reviews of radioactive technics and of their varied applications have been prepared by Evans,[11] Greenberg,[12] Hamilton,[13] Hevesy[14] and Lawrence.[15]

Phosphorus

Radioactive phosphorus was the first of the isotopes to be applied to investigations of animal metabolism, and was used by Hevesy and his associates[14, 16] to study the absorption and distribution of phosphorus in rats, and to trace the formation of phospholipids and other phosphorus-containing organic substances in various tissues. During the seven years since this work was reported, over a hundred papers have appeared dealing with the application of this technic to studies of phosphorus metabolism. It was found that inorganic phosphates were readily absorbed from the upper intestinal canal, and were quickly converted into organic phosphorus compounds.[17–19] Phospholipids were synthesized most rapidly in the liver, kidney and intestinal wall and more slowly in other organs and tissues.[20] Phospholipid synthesis was apparently carried on in each tissue independently of similar activity in other organs,[21] and continued in tissue slices in vitro.[22] The rate of phospholipid turnover was definitely influenced by the level of lipids in the circulating blood, being accelerated when fats were absorbed from the intestine.[21]

Various foodstuffs greatly influence the deposition of fat in the liver, and considerable interest has arisen concerning the role that these substances play in preventing or producing liver disease. The mode of action of such substances has been studied with the use of radioactive phosphorus as an indicator of phospholipid formation. It was found that the increase in liver fat produced by the feeding of cholesterol was associated with a decrease in the rate of formation of new phospholipid, although the total phospholipid content of the liver was not changed.[23] Choline, cystine and methionine (lipotropic substances) produced an opposite effect, — that is, a decrease in total liver fat and an acceleration in turnover of phospholipid,[24–26] — whereas other amino acids had no such effect.[27] It thus appears that the substances controlling deposition of lipids in the liver exert their effect by influencing phospholipid turnover.

The major portion of any given dose of radioactive phosphorus is eventually deposited in the bones.[28, 29] Therefore, the structures in close proximity to bone, such as the marrow, are subjected to localized bombardment by the beta rays given off by the decaying isotope. The first observations of the effect of such radiation were made by Scott and Cook,[30] who fed large doses of radioactive phosphorus to chicks and found a subsequent decrease in the number of circulating leukocytes. This observation suggested that radioactive phosphorus might be a valuable therapeutic agent in diseases in which there was abnormal

growth of leukocytes, such as leukemia. Lawrence and Scott[31] and Lawrence, Tuttle, Scott and Connor[32] investigated the effect of radioactive phosphorus on mice with leukemia, and found that it decreased the number of abnormal leukocytes in the circulating blood, and that the uptake of radioactive material by leukemic lymph nodes and spleens was three times greater than the uptake by normal lymph nodes and spleens. Subsequent studies showed that the rapid assimilation of radioactive phosphorus by tumor tissue was merely a reflection of its rapid metabolism, and was not a peculiarity of the tumor tissue itself.[33–40] However, the concentration of the radioactive material in neoplastic tissue subjected it to localized, in situ radiation, with resultant selective destruction of tumor cells, and explained the beneficial effect of radioactive phosphorus on animals with experimental leukemia.

These findings led to the therapeutic administration of radioactive phosphorus to human beings with leukemia, and in general the results were similar to those observed in animals with experimental leukemia. Patients with leukemia and polycythemia retained more radioactive phosphorus than normal persons, and it was concentrated in tumor tissues, leukemic leukocytes and leukemic bone marrow,[41–43] where it was built into nucleoproteins and phospholipids.[39, 40] The leukemic cells in the bone marrow, lymph nodes and peripheral blood were thus subjected to fairly specifically localized and intense radiation.

Erf, Tuttle and Lawrence,[44] who have recently summarized their clinical experiences with radioactive phosphorus in 100 cases of leukemia, believe that this form of therapy has distinct advantages over x-radiation because of the ease with which it can be administered (either by mouth or by intravenous injection), and because of the freedom from subsequent radiation sickness and skin reactions. They observed no clinical improvement in the patients with acute leukemia who were treated, although Warren[45] reported definite improvement in certain patients with acute leukemia treated with intravenously administered radioactive phosphorus. The results in chronic leukemia were more encouraging[44]: of 63 patients treated with radioactive phosphorus, 19 showed clinical improvement lasting from three to twelve months, 6 were completely well with normal laboratory findings for periods ranging from three months to two and a half years, and 2 were apparently completely cured and still living after two years. Investigators[46] at the Memorial Hospital in New York also found radioactive phosphorus a good and reliable therapeutic agent for lymphosarcoma and for chronic myelogenous and lymphatic leukemia, although it proved of little benefit in acute leukemia and in various other neoplastic diseases.

The natural history of leukemia, with its frequent remissions and exacerbations, necessitates extreme caution in evaluating the results obtained from any form of therapy, and since radioactive phosphorus has been used extensively for the treatment of leukemia for only two years, it is hazardous to draw too sweeping conclusions regarding its actual advantage over other forms of radiation therapy. Careful review of the reported cases indicates that the end results were little different from those that would have been obtained with x-radiation.

Six patients with polycythemia vera have been treated with radioactive phosphorus.[47] Considerable clinical improvement was noted, and there was some reduction in the erythrocyte count and hemoglobin level. The benefits obtained do not appear to have been superior to those that could have been achieved with the much less expensive and simpler procedures of restricting iron intake and performing phlebotomies.

All in all, radioactive phosphorus therapy appears to be a convenient but expensive method of administering radiation therapy to patients with leukemia and polycythemia. The results obtained are at least as good as those to be expected from x-ray treatment, and the technic definitely merits further investigation.

Iron

For many years, there has been considerable controversy concerning the absorption and excretion of iron, and the most favorable form of the element for therapeutic use. Since it was impossible chemically to distinguish between iron that passed through the intestinal canal unabsorbed and iron that might have been excreted into the intestine, some investigators claimed that large quantities were absorbed and re-excreted, whereas others found that absorption did not take place in normal persons. With the use of radioactive iron, this problem has been solved, since the exact fate of a particular dose of iron can be determined accurately. Hahn and his collaborators[48] applied the radioactive tracer technic to the study of iron metabolism in dogs, and found that normal and plethoric animals absorbed very little iron, and that anemic animals assimilated considerable quantities. Moreover, iron absorption was controlled by the state of iron reserves in the body and not by the anemia per se, since animals made acutely anemic absorbed no more iron than they did when their blood levels were normal, and it was only after depletion of the iron stores in the tissues that iron was taken up from the bowel.[49]

Ross and Chapin[50] found that normal human subjects absorbed very small amounts of iron, although patients with the hypochromic anemia of

iron deficiency took up much larger amounts. Patients with untreated pernicious anemia, a condition in which the iron reserves of the body are adequate in spite of marked anemia, absorbed no more iron than normal subjects. However, the same patients took up considerable quantities of iron after treatment with liver extract and after depletion of body reserves of iron, even though the anemia had been relieved and was of minimal degree. The ferric, ferrous and reduced forms of iron were absorbed and utilized for hemoglobin formation with equal rapidity and facility.[51, 52] Insignificant amounts of iron were excreted in the urine and bile, and only minute amounts were eliminated in the feces under normal conditions, several years being required to excrete a surplus of iron equivalent to the total iron content of circulating hemoglobin.[53] These studies indicate that human subjects and experimental animals control iron metabolism by regulating the amounts of iron absorbed and not, as was formerly believed, by varying the amount excreted. In some way as yet unexplained, iron absorption occurs only when the reserves of tissue iron are depleted.

After absorption, radioactive iron is incorporated into the hemoglobin molecule with extreme rapidity, and is released into the circulation in newly formed erythrocytes within a few hours after ingestion.[51, 54] Once built into the hemoglobin molecule, radioactive iron is "fixed" within the erythrocytes,[55] and has provided a new method for studying cell and blood volume, since the total volume of blood or cells can be calculated from the degree of dilution of a known number of tagged cells injected into the vascular system of experimental subjects. With the use of cells labeled in this way, it has been found that the total volume of cells in the vascular system is less than was formerly supposed, and that very few if any cells are immobilized in the spleen or elsewhere in the body.[56, 57] The concept that the spleen serves as a reservoir for erythrocytes that can be mobilized in times of stress is thus subjected to serious doubt, and the increase in hematocrit produced by administration of adrenalin is probably caused by a redistribution of cells and plasma in the vascular system.

Further application of the radioactive tracer technic should clarify many problems of hemoglobin and iron metabolism, and the use of erythrocytes tagged with radioactive iron may be of considerable value in studying the changes in blood volume that occur in shock, cardiac failure and pregnancy.

Iodine

By means of radioactive iodine, it has been possible to follow the uptake of iodine by the thyroid gland, and to detect differences in iodine metabolism in various types of thyroid disease.[58] When a suitably designed radiation detector was placed over the thyroid gland, and the patient then fed radioactive iodine, the rate of deposition of the radioactive material in the thyroid was registered on the counter. Normal subjects took up an amount of iodine approximately equivalent to that already present in the gland, and a maximum concentration was reached in about two days. This concentration was then maintained at a fairly constant level for the ensuing thirty days. In marked contrast to the normal glands, hyperactive glands of patients with Graves's disease assimilated four or five times more iodine, and took it up at an extremely rapid rate, the maximum concentration being reached in approximately four hours. The rapid uptake was followed by a rapid loss of iodine during the next few hours; this fact indicated that the mechanism by which the hyperactive gland stored iodine was much different from that of normal glands. Nontoxic goiters took up larger quantities of iodine than normal glands, but the rates of uptake and storage were very similar; iodine metabolism in nontoxic goiter was accordingly not significantly different from that of the normal gland. Atrophic glands of patients with myxedema took up only very minute quantities of iodine. Very recently, Hertz and Roberts[59] have employed the differential rates of iodine uptake by thyroid glands to distinguish between two types of hyperthyroidism that they classify as "ophthalmopathic" and "classic" Graves's disease.

Pretreatment with iodine markedly decreased the subsequent uptake of iodine by both normal and hyperactive glands.[60–62] This information has been applied clinically with the discovery that a single large dose of iodine produces the same therapeutic effect in Graves's disease as repeated massive iodinization.[61] This suggests that the common clinical practice of administering Lugol's solution to patients with Graves's disease for weeks prior to thyroidectomy is unnecessary, a single large dose probably being about as effective.

The exact sites of localization of iodine in thyroid tissue can be determined by the unique technic of "radio autography." When thin sections of thyroid tissue containing radioactive iodine (removed from patients previously fed radioactive iodine) are placed on sensitive photographic plates, the beta rays liberated by the iodine expose the plate, the heaviest exposure being produced in regions in which the radioactive iodine is most concentrated. If these tissue sections are then stained and examined histologically, the areas of exposure on the photographic plate can be identified with the corresponding areas in the tissue, and the exact site of localization of the iodine easily determined.[63] Such studies show that iodine

is deposited in equal concentrations in the colloid and cells of active glands. However, carcinomatous thyroid tissue does not take up iodine. It is thus impossible to administer therapeutic radiation to this neoplastic tissue in situ, in the way that radiation can be given to leukemic tissue with radioactive phosphorus. On the other hand, since radioactive iodine does localize in hyperplastic thyroid tissue, Hertz and his associates[60] are employing radioactive iodine therapeutically in patients with Graves's disease. Considerable amounts of radiation can be administered in situ in this way, and it is hoped that this radiation will serve to inhibit the overactivity of the parenchymal cells, and thus reduce the overproduction of thyroid hormone.

Sodium and Potassium

Radioactive sodium and potassium have been used extensively in the study of the permeability of various cell membranes to cations, and the essential extracellular nature of sodium and the intracellular character of potassium have been verified. Radioactive sodium entered the intracellular phase of sodium-containing tissues in proportion to the sodium content of the tissue — an indication that the cell membranes of such tissues are not completely impermeable to sodium.[64] Erythrocytes are permeable to both potassium and sodium ions,[64-68] and the classic theory of cation impermeability of the erythrocyte must therefore be considered as relative only. The cell membrane is undoubtedly more permeable to anions than it is to cations, but cations do penetrate it, and the difference in concentrations of cations inside and outside the cell must be due to some mechanism other than mere membrane impermeability.

Zwaardemaker[69] advanced the theory that the physiologic activity of some elements might be due to their natural radioactivity, and suggested that the intrinsic rhythmicity of the heart beat might be caused by the radiations given off by the naturally occurring isotope of potassium. He believed that the cessation of the heart beat produced by removal of potassium from perfusing fluid was due to the removal of these radiations. Glazko and Greenberg[70] effectively disproved this theory by replacing the potassium of perfusing fluid with radioactive sodium, which supplied infinitely more radiations than the naturally occurring radioactive potassium but which did not maintain cardiac rhythmicity. Various radioactive substances produced no immediate physiologic changes, even when the amount of radioactivity administered was very large.[71]

The possibility that neoplastic disease is caused by the concentration of naturally occurring radioactive potassium in tissue has been investigated by Lasnitzki,[72] who found that radioactive potassium was present in identical concentration in all tissues studied, both normal and neoplastic. The same investigator[73] has recently reported, however, that the light, stable isotope of potassium (K^{39}) is concentrated in tumor tissue, and in normal muscle tissue of tumor-bearing animals.

Since sodium is essentially extracellular in distribution, a method of determining extracellular fluid volume with radioactive sodium has been developed.[74] By this procedure, the average extracellular volume of human subjects was found to be 17.7 liters, or 23.5 per cent of the body volume. Approximately 85 per cent of this fluid was extravascular, and 15 per cent intravascular. Because of technical difficulties, this method is not so practical as the simpler thiocyanate one in general use.

Calcium and Strontium

Calcium and strontium are members of the same group in the periodic table of elements, and Pecher[75, 76] has found that radioactive calcium and radioactive strontium are distributed and metabolized in the animal organism in a similar fashion. Both are deposited in the skeleton, particularly in trabecular bone, epiphyses and regions of active skeletal growth.[77] The beta rays given off by radioactive calcium are too weak to be of value therapeutically, but the energetic beta particles emitted by radioactive strontium are capable of producing considerable tissue ionization, and should be of definite value in destroying neoplastic tissue. Consequently, since radioactive strontium is deposited in the newly formed osseous tissue of bone tumors, it is being used in the treatment of osteogenic sarcoma with the hope that radiation liberated in situ will be more effective than external x-radiation.[75]

Carbon

The carbon dioxide formed by the metabolism of the animal organism has been considered a waste product, and the animal organism was believed to be entirely dependent on the plant kingdom for conversion of inorganic carbon to organic forms suitable for foodstuffs. The recent work of Conant, Hastings and their associates[4, 78] indicates that this concept must be revised, and that the animal organism can use inorganic carbon dioxide for the formation of carbohydrates. Lactic acid containing radioactive carbon was fed to starved rats, and after two and a half hours, glycogen was isolated from the liver and assayed for its content of radioactive carbon. Although the amount of glycogen formed corresponded to 30 per cent of the lactate administered, only 1.6 per cent of the administered radioactive carbon was found in this newly formed glycogen; this indicates that the carbon used for synthesizing this glycogen did not originate directly or solely from the lactic acid molecule. This carbon must therefore have been

derived from some endogenous source, probably carbon dioxide. Subsequently, by injection of sodium bicarbonate containing radioactive carbon into starved rats, it was found that considerable amounts of the labeled carbon from the bicarbonate had been deposited in the liver as glycogen. It thus appears that the carbon dioxide liberated by carbohydrate catabolism is not entirely a waste product, but can be reutilized in the liver for formation of new glycogen.

Sulfur

Sulfur compounds play a very significant role in numerous oxidation-reduction reactions in the body, and the essential nature of methionine, cystine and thiamin is well established. However, the intermediary metabolic reactions of these substances and their eventual fate in the body are still obscure. Using radioactive sulfur as a label, several investigators have studied the reactions of these substances in the body. Ingested inorganic sulfur apparently exchanged with the sulfur of the tissues to some extent, since its complete excretion was delayed.[79] It was not incorporated into cystine, however, and the sulfur of cystine did not exchange with inorganic sulfur.[80, 81] Thiamin (vitamin B_1) containing radioactive sulfur was rapidly destroyed by both normal and thiamin-deficient human subjects.[81] Approximately 10 per cent of the body's content of vitamin B_1 was broken down every twenty-four hours.[83] When thiamin was injected into subjects maintained on a normal diet, there was a very large wastage, 61 per cent appearing in the urine and 11 per cent in the feces within a few hours.[82, 83] These findings indicate the probable futility of attempting to increase the body's stores of thiamin above the normal level.

Cobalt, Copper, Manganese and Zinc

Minute amounts of cobalt, copper, manganese and zinc are essential for the normal health and nutrition of animal organisms, but little is known of the exact roles that they play in metabolic processes. The radioactive isotopes of all these elements are easily prepared and detected, and afford an entirely new method of investigating their biologic activities. At present, they have been employed only for the study of absorption and excretion in animals,[84–86] but it is probable that they may soon be used in investigations of various essential enzyme systems.

Arsenic

Arsenical compounds are valuable therapeutic agents in syphilis and in various parasitic infections, although little is known of their distribution or mode of action. With the intention of determining their action in these diseases, several investigators[87, 88] have made careful preliminary studies of the distribution of such compounds in various animals. Soon after injection, arsenic is concentrated in the liver, kidneys and lungs, but subsequently is so rapidly excreted in the urine that only minute amounts remain in the body after one week.

* * *

Radioactive isotopes have been employed extensively as indicators of metabolic activity in experimental animals, and have been of greatest value in elucidating fundamental problems of normal physiology. The isotopic tracer technic has been applied to the study of disease in human beings only during the last three or four years, but already has resulted in significant improvement in the therapy of several metabolic and neoplastic diseases. Extension of the technic to other diseases will undoubtedly lead to a better understanding of underlying pathologic physiology and indicate new and better forms of treatment.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28211

PRESENTATION OF CASE

A sixty-three-year-old businessman was admitted to the hospital because of fever, cough, chest pain and sputum.

The patient had been in fair health except for "arthritis," some malnutrition and a chronic cough that was productive of about a cupful of sputum a day during the six months before entry. Two days before entry, following exposure to cold, he experienced a shaking chill followed by fever and pain in the front of the left chest; this was made worse by breathing. The sputum became tinged with blood.

The patient drank much alcohol until four years before entry and ate very poorly. The more remote history was not available.

Examination showed an acutely ill man, flushed and dyspneic with dusky cyanosis. There was dullness in the left midaxilla extending to the left base posteriorly, where breath sounds were diminished, with a suggestion of bronchovesicular breathing and rhonchi. There was a questionable friction rub. The heart seemed normal. The abdomen was very slightly distended.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 99.5°F., the pulse 112, and the respirations 31.

Examination of the blood showed a red-cell count of 3,620,000 with 11.3 gm. hemoglobin, and a white-cell count of 18,000 with 90 per cent polymorphonuclears, 7 per cent lymphocytes and 3 per cent monocytes. The blood Hinton reaction was negative. The urine showed a ++++ test for albumin, a specific gravity of 1.010 and a sediment containing numerous white blood cells with rare casts and red cells and no bacteria. A Type 9 pneumococcus was identified in the sputum by the Neufeld reaction.

Roentgenograms of the chest showed generalized increase in linear markings throughout the right lung field and in the upper portion of the left lung field. The lower part of the left lung field was homogeneously dense, and in the lateral view showed numerous areas of consolidation in the region of the left lower lobe. There was much calcification in the aorta.

The patient was treated with small doses of sulfadiazine and did fairly well for two days. The temperature ranged from 98.6 to 100°F. The urine remained filled with white blood cells and albumin. On the third hospital day, there was gross hematuria, and the patient complained of pain in the left flank. No crystals were evident in the urine, and the sulfadiazine blood level had reached a maximum value of only 8 mg. per 100 cc. The nonprotein nitrogen was 56 mg. per 100 cc., rising to 75 mg. two days later. Intravenous glucose in physiologic saline solution was given in four clyses. On the fifth hospital day, there was complete dullness over the left lower lobe, with diminished breath sounds. The next day, extreme dyspnea appeared. The temperature spiked to 102°F. for one reading. Bubbling rales became audible in both lung fields. On the eighth day, the patient became cyanotic, and the systolic blood pressure dropped to about 100. The urinary output became less than 500 cc. per day, with a specific gravity of 1.006, a + test for albumin and many red cells and a few unidentified crystals in the sediment. The nonprotein nitrogen rose to 102 mg. per 100 cc. Cheyne-Stokes respirations appeared, and the patient expired the following day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN H. TALBOTT: This patient had an exudative respiratory disturbance for six months and an acute respiratory disease for two days. We have no further information about the "arthritis," the anemia or the cause of the malnutrition. He had been a heavy imbiber of alcoholic beverages. These facts are probably incidental to the malady responsible for death. The association of arthritis and kidney disease makes one raise the question of gout, but I think we can dismiss it without further consideration. There is no evidence that the patient had cirrhosis of the liver, which one might suspect on the basis of the alcoholic history. There are no data about urinary symptoms or other evidence to suggest a nephritis. The first evidence of kidney disease was observed on admission to the hospital; this was in addition to an acute pulmonary process. Nothing is stated about the examination of the fundi. We do not know whether there were any retinal changes, which are most important diagnostically in a consideration of a kidney lesion. I realize that a patient who comes in with pneumonia may have a very cursory examination of the eyegrounds. Was any statement made in the record about a retinitis?

DR. TRACY B. MALLORY: There is a check against "fundi" on the chart, which should mean that they were looked at and nothing found.

DR. TALBOTT: The patient had clinical signs of pneumonia and a white-cell count of 18,000. The

temperature was 99.5°F., the pulse 112, and the respirations 31.

I should like to see the x-ray films.

DR. MALLORY: The films were lost.

DR. TALBOTT: I was afraid something like that would happen, having hoped that we should get additional information, from the interpretation of the x-ray films, whether or not there was pulmonary edema such as might be seen in acute nephritis.

We must be content with what we are given in the record. The absence of clubbing of the fingers makes one disinclined to attribute too much significance to the chronic cough, such as might be associated with bronchiectasis or advanced pulmonary fibrosis. Undoubtedly, this patient had a chronic pulmonary process as well as an acute one. There was no history of exposure to tuberculosis, no examination of the sputum for tubercle bacilli, and no history of hemoptysis. I am inclined to make a diagnosis of chronic nontuberculous pulmonary infection, which was probably exaggerated by bronchitis in the six months before admission and was responsible for the expectoration of a cupful of sputum daily. The acute process was probably a pneumococcal pneumonia.

DR. MALLORY: The X-ray Department did call it pneumonia.

DR. TALBOTT: Now we come to the kidneys. It is stated that the patient had small doses of sulfadiazine, and yet the blood level rose to 8 mg. I think one can say that some renal impairment must have existed to give a blood level of 8 mg. on small doses of sulfadiazine. The onset of pain in the left flank, followed by hematuria and a rising nonprotein nitrogen, makes me believe that this patient had renal impairment secondary to sulfadiazine toxicity. Renal involvement following sulfadiazine ingestion is not so common as it is with some of the other sulfonamides. Two conditions may predispose to the development of a sulfadiazine reaction in the kidney: a patient may develop a sensitivity to the drug because of previous ingestion; and probably much more important clinically is the presence of a pre-existing renal disease. A patient who has a pre-existing renal disease is more prone to develop renal toxicity from any of the sulfonamides. The acute episode on the second day was, I believe, associated with sulfadiazine damage to the kidney, and I think we are going to find, if the kidney was prepared properly, plenty of evidence of sulfadiazine crystals microscopically.

So far as the mechanism of renal damage from sulfonamides is concerned, it is probably a combination of toxic damage to the parenchyma of the kidney and plugging of the convoluted tubules by precipitated crystals. Patients who develop a sulfonamide reaction may have complete shutdown of one or both kidneys. The sulfadiazine reaction was treated with intravenous glucose and physiologic saline solution. I have two comments to make in this connection. I think that the use of saline is undesirable in sulfonamide anuria. The solubility of sulfonamides is depressed in a urine of high salt content. If urine formation is resumed, the tendency to further precipitation is augmented. Moreover, intravenous saline solution may cause some edema of the tubules and delay restoration of function. I think a patient with a sulfadiazine reaction should probably get glucose and not saline solution. The question of alkalinity of body fluids, particularly urine, has been raised in connection with sulfadiazine reactions in the kidney. There is conflicting evidence in the literature concerning whether or not an alkaline urine is less harmful to a damaged kidney than an acid one. Indirect evidence is based on renal damage from transfusion, in which the precipitation of hemoglobin, or rather the damage from precipitation of hemoglobin, is less with an alkaline than with an acid urine. On the basis of this and other experimental evidence, I should have recommended either soda by mouth or sodium lactate intravenously and continued alkalinization of the patient until most of the evidence of kidney damage had disappeared.

What is the prognosis in renal toxicity due to sulfadiazine? This patient died. If he had not had an overwhelming malady, I do not believe that the kidney damage itself would have ended fatally. Did he die of pneumonia alone? I do not believe so. I think it was a combination of renal disease and pneumonia. The renal disease was also a combination of sulfadiazine reaction superimposed on the pre-existing kidney disturbance.

What was the nature of this kidney disturbance, which was manifested by a ++++ test for albumin on admission and a + test for albumin on one or two subsequent occasions? The patient had a specific gravity of 1.010 on admission and yet presumably was dehydrated. One can assume that any patient who has pneumonia is probably dehydrated by the time he comes to the hospital. The sediment contained many white cells, but no red cells were noted until after the ingestion of sulfadiazine.

Was this an acute or a chronic nephritis? If it were the former, it might be associated with a bronchitis. We have no evidence — from the eyegrounds, from the blood pressure or from past history of kidney disease — whether or not any-

thing had been going on in the kidney before admission to the hospital. I do not believe I can go any farther in differentiating the primary renal lesions in this patient beyond affirming that there was something that predisposed to the sulfadiazine toxicity. In conclusion, I think we have two conditions in the lungs, and two in the kidneys. In the kidney, there was an underlying nephritis, with a superimposed sulfadiazine reaction.

DR. FLETCHER COLBY: Could not the left-sided renal pain with gross hematuria be explained in some other way than by a drug reaction — that is, by something such as a renal infarct? Gross hematuria and pain in a sulfadiazine reaction are unusual, it seems to me, especially when we do not find crystals in the urine. I do not remember any patients with gross hematuria from sulfadiazine, and I do not remember any who have had pain as the prominent symptom.

DR. TALBOTT: Do you think that the ureter was plugged on that side?

DR. COLBY: I do not know.

DR. CHAMP LYONS: I do not believe we know everything about the renal complications of sulfonamide therapy. The kidney content of sulfanilamide and sulfadiazine is apparently a reflection of the blood concentration of the drugs, but sulfathiazole and sulfapyridine may be present in the kidney in concentrations above the blood content of sulfonamides. Two types of renal complications occur: one is a toxic effect on the tubules, and the other results from the precipitation of crystals of the free or conjugated drug; both produce hematuria. Sulfathiazole and sulfapyridine crystals may precipitate out and obstruct the kidney tubules, pelves or ureters, but sulfadiazine crystals, in my experience, are limited to the pelvis and ureter — they do not precipitate in the kidney tubules. Hence, in sulfadiazine therapy, the presence of crystals and blood in the urine suggests ureteral obstruction by crystals. In this case of hematuria without crystalluria, I should consider the kidney lesion an acute toxic nephritis due to sulfadiazine or some other agent.

DR. TALBOTT: You think the pain might come from a toxic reaction rather than from the crystals? I had attributed it to the formation of crystals.

DR. LYONS: Left costovertebral pain and tenderness may occur without crystal formation. In painful crystalluria due to sulfadiazine, there is usually the flank pain of ureteral colic. I am here to see what Dr. Mallory is going to say about the kidneys, because I am puzzled about the clinical interpretation of hematuria in sulfonamide therapy.

DR. ALLAN M. BUTLER: I missed the rationale of the alkalinization of this patient. Did Dr. Talbott want to give him alkali to provide the maximum solubility for the hemoglobin or for the sulfadiazine in the urine or for some general reason because of the presence of renal damage?

DR. TALBOTT: The last two, in the presence of hematuria.

DR. BUTLER: If it is the last two, I should question the wisdom of alkali, because I do not believe we have very definite evidence that alkali within the pH range of urine changes to any appreciable degree the solubility of any known sulfadiazine derivatives.

DR. LYONS: Then you have not accepted Flippin's[1] results on the diminished incidence of crystalluria in patients receiving soda bicarbonate along with sulfonamides?

DR. BUTLER: For the reason that, if I remember the paper, he had no control of the urine volume. Is that the one he read at the meeting of the American College of Physicians last spring?

DR. LYONS: Yes.

DR. TALBOTT: According to reports in the literature,[2,3] the acidity of the urine is a most important factor. The solubility of a sulfonamide at pH 7.5 is nearly double that at pH 6.0. This fact should be appreciated by all who use the drugs, since alkalinization of the urine is a simple and harmless procedure.

DR. BUTLER: The work of Sunderman and Pepper[2] indicates some increase in the solubility of sulfathiazole. The bulk of evidence shows no increase in that of sulfanilamide or sulfapyridine. So far as I know, there is no quantitative evidence for sulfadiazine.*

DR. LYONS: I believe the clinical observation of decreased incidence of crystalluria is sufficient to make it likely that alkalinization may increase the solubility of free sulfonamide crystals without affecting the conjugated sulfonamide derivatives.

DR. BUTLER: I agree that there is a possibility, because there is considerable evidence that there are derivatives of sulfonamides excreted in the urine whose identity has not been established; such derivatives may have an increased solubility with a pH of 7.8.

DR. LYONS: Do you agree that the present evidence warrants the alkalinization of the patient? Is that unfair to assume?

DR. BUTLER: I am not sure. According to the third criterion, you apparently believe you are doing something to protect the injured kidney by alkali. Does anyone know whether that is so?

DR. TALBOTT: In a transfusion reaction, we are certain that alkali helps.

*Dr. Butler reports that since this conference he has learned of unpublished work showing that the solubility of urinary sulfadiazine may increase as much as fivefold, with an increase in urinary pH from 5.5 to 7.8. He has therefore requested that this information be added to this discussion, since it suggests that urinary alkalinization should specifically be beneficial with sulfadiazine therapy.

DR. BUTLER: There, one is dealing with the first criterion, when alkalinization does make sense. But does it for the third purpose?

DR. MALLORY: The patient under discussion did not have hemoglobinuria but hematuria.

CLINICAL DIAGNOSES

Lobar pneumonia (Type 9 pneumococcus).
Nephritis.
Uremia.

DR. TALBOTT'S DIAGNOSES

Chronic nontuberculous pulmonary infection.
Pulmonary fibrosis.
Pneumococcal pneumonia, Type 9.
Sulfadiazine reaction.
Nephritis, ? acute or chronic.

ANATOMICAL DIAGNOSES

Lobar pneumonia.
Chronic pulmonary fibrosis, with emphysema.
Acute glomerular nephritis.
Arteriosclerosis, aortic and iliac.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed evidence of old chronic pneumonitis, with extensive pulmonary emphysema and fibrosis. It also showed a lobar pneumonia in the left lower lobe and extensive fresher pneumonia scattered throughout the other lobes. The kidneys were a little large, weighing 400 gm. When the capsule was stripped backward, the surface puckered somewhat, indicating that the substance was slightly edematous. The capsule stripped very easily, disclosing surfaces that showed a few red flecks. Most careful examination of the pelves, of the ureters and of the substance of the pyramids and cortex under the dissecting microscope showed no crystals anywhere. Microscopic sections showed a very acute glomerulonephritis, but characteristic enough so that I have not the slightest doubt about the diagnosis and there is no evidence of tubular damage.

DR. TALBOTT: You found no microscopic evidence of sulfadiazine toxicity?

DR. MALLORY: I should doubt if the drug ever got through the glomeruli.

DR. BUTLER: Did the picture account for the number of white cells in the urine?

DR. MALLORY: Not too well; it accounted for the gross hematuria well enough, and pain in the back is not uncommon with an acute glomerulonephritis.

DR. BUTLER: Was there a good deal of what Addis[4] calls "degenerative changes"?

DR. MALLORY: Not much—the lesion was too acute. The average glomerulus contained thirty to fifty polymorphonuclears, whereas seven to twelve is about the normal number. There was also definite, though early, proliferation of endothelial nuclei. I do not believe one can seriously question the diagnosis of glomerulonephritis.

DR. LYONS: Feinstone and his co-workers[5] reported only tubular nephritis from sulfadiazine. Is it possible that sulfadiazine could cause glomerular damage?

DR. MALLORY: I am reluctant to believe any chemical substance can cause glomerular nephritis. I would rather believe that the sulfonamide so altered the immune reactions of the body that the latter reacted to a pneumococcus as if it were a streptococcus.

DR. BUTLER: How sure are you that the preparations in which the kidney was fixed did not destroy the sulfadiazine crystals?

DR. MALLORY: We looked for crystals with the dissecting microscope in unfixed tissue.

DR. TALBOTT: There were no crystals in the sections?

DR. MALLORY: No; in other cases of sulfonamide nephrosis, we have had no difficulty finding the crystals, usually in large numbers in the pelvis and frequently in significant numbers in the renal parenchyma.

DR. TALBOTT: Do you routinely put them in absolute alcohol?

DR. MALLORY: We have had no luck in preserving crystals in sections with any fixative or embedding method.

DR. ALLEN G. BRAILEY: Is it not possible to get a double infection, streptococcal as well as pneumococcal?

DR. MALLORY: I suppose that is conceivable.

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CASE 28212

PRESENTATION OF CASE

A sixty-seven-year-old Portuguese-American fisherman was admitted to the hospital because of abdominal pain of several hours' duration.

The patient was essentially well until the night before entry, when he noted gradual onset of periumbilical pain, which rapidly became worse. The pain was sharp, severe and fairly steady, although it was worse when gurgling occurred in the abdomen. On the morning of entry, the pain subsided and shifted to the midline below the

umbilicus. The patient vomited once, regurgitating only food that he had eaten that morning. During the illness, he passed neither gas nor feces.

Twelve years before entry, he was operated on for "stomach ulcers" at a community hospital, following four days' study. Subsequently he had frequent attacks of gas pains in the upper abdomen, which were always relieved by the taking of food. These pains were similar to the one that brought him to the hospital except that this last attack was not relieved by food.

On admission, the patient appeared well developed but thin. He was groaning from pain. The abdomen was distended and tympanitic, with diffuse spasms of the muscles. Although the markings of loops of bowel were visible, there were only occasional bursts and tinkles of high-pitched, loud peristalsis. There was dullness in both flanks, which appeared to shift when the patient was lying on his side. No masses were palpable. Tenderness seemed to center in the left upper quadrant. Rectal examination demonstrated a bulging, soft, boggy posterior cul-de-sac, which was not tender. There were no feces or gas in the rectum. The heart and lungs seemed normal.

The blood pressure was 160 systolic, 90 diastolic. The temperature was 99.5°F., the pulse 88, and the respirations 20.

Examination of the blood showed a white-cell count of 13,000. The blood Hinton reaction was negative. The urine was normal. An abdominal roentgenogram showed several loops of markedly dilated small bowel in the midabdomen and left upper abdomen.

On the second hospital day, an operation was performed.

Differential Diagnosis

Dr. Reginald H. Smithwick: In general, the history seems to be that of a patient suffering from obstruction of the small intestine. Various characteristics of the pain suggest that it originated in the small bowel. In the first place, it was in the midline, in the region of the umbilicus. That would place it somewhere in the middle of the tract of the small intestine, perhaps below that point. It was gradual in onset rather than sudden. That probably is of some significance, since it tends to make certain causes for small-bowel obstruction less likely than others, such as mesenteric thrombosis and volvulus. The abdomen was distended, and there were visible loops of intestine. The x-ray films certainly appear to be consistent with tremendously dilated loops of small bowel. Only one statement is a little upsetting, and that is the description of the diffuse spasm of the muscles. That is unusual in simple obstruction of the small bowel, in which, unless complications have taken place, there is generally a notable absence of spasm. Unless the peritoneum is involved by infection, spasm, at least of an involuntary nature, will not occur. We know that if one puts a balloon in the small bowel and distends it so that very severe peristaltic pain is initiated in normal human beings, there is absolutely no spasm whatever; the abdomen is soft and flaccid. However, it is possible for certain persons to react to pain by voluntary spasm, and I am rather inclined to think, because of the essentially normal temperature, blood count and other evidence that does not point to infection, that the spasm described was probably voluntary and not involuntary, and was simply a reaction of the patient to discomfort.

The pain was periumbilical in the beginning and shifted to the midline below the umbilicus. That may be of some significance and might possibly indicate that whatever was the cause of the obstruction had moved downward a little bit. Also, because the pain subsided after admission, the patient's condition may have improved temporarily, and the degree of distention within the intestine may have become less. What relation this obstruction had to the previous history of operation for ulcers is problematical; since no details are given concerning the previous operation, it is perhaps not worth while for me to speculate about, except to say that gastric ulcers may become malignant and that the patient might have developed peritoneal metastases, although his state of well-being before the sudden onset of this illness is against that.

It is possible that this patient had an asymptomatic lesion elsewhere in the abdomen, in the large bowel, for example, to which the small bowel had become adherent and secondarily obstructed. We may exclude hernia as a cause of small-bowel obstruction, because there is no evidence of that. The next most likely cause is adhesions or bands following operation or previous inflammatory disease in the abdomen. In any patient who has had a previous operation and has had repeated attacks of crampy abdominal pain ever since, the possibility of adhesive bands as the cause of small-bowel obstruction, even after twelve years, must be considered, on statistical grounds, as very likely.

Other causes of small-bowel obstruction are tumors, which are not very common in the small bowel, such as a polyp, which might result in intussusception and cause such a picture. Foreign body must also be considered. The patient had a past history of some indigestion. He may have had gallstones, and it is possible that he passed a stone into his duodenum and that it later became impacted in the ileum. Stricture of the bowel from an old inflammatory lesion, such as tuberculosis, or ulceration of some other nature might

be the cause of repeated attacks of small-bowel pain culminating in obstruction such as this. Cancer of the small bowel, carcinoma, sarcoma and lymphoma are quite rare but might be present.

Other possible causes that might be mentioned are changes in the circulation—an embolus, for example, since the patient is in the arteriosclerotic age, or mesenteric thrombosis. These usually are a little more severe and intense and more sudden in origin and are usually accompanied by a higher white-cell count than this man had and usually do not tend to improve once they have become well established. The nervous causes of intestinal obstruction are rare, but they are not unknown. We have recently had a patient who had such a small-bowel obstruction,—very possibly from a derangement of autonomic and vagus activity,—but ileus of that nature is usually secondary to a lesion elsewhere, such as one of the biliary or genitourinary tract.

It seems unlikely to me that this patient had pancreatitis, perforated ulcer, renal or biliary colic or a lesion of that sort. The symptoms are consistent with a diagnosis of middle or low small-bowel obstruction whose cause is not entirely clear, but I think, on the chances, one would have to put postoperative obstruction or obstruction due to an adhesive band as first choice.

Dr. Arthur W. Allen: We connected the acute small-bowel obstruction with the previous surgery. We knew that the patient had had some sort of operation on his stomach. We did not know what kind. Dr. Charles Mixter, Jr., made a very excellent effort to get the Miller–Abbott tube into the small bowel under the fluoroscope. It seemed to leave the stomach and go to the right for a certain distance, but no farther, and then bounce back into the stomach. Consequently, without waiting and struggling with it any more, we decided that we had better explore the patient, since our experience with Miller–Abbott tubes that fail to pass the pylorus readily in small-bowel obstruction has been very unfortunate. If we had waited until morning, I think we could not have rescued this man because we could not have decompressed the small intestine with the Miller–Abbott tube.

At operation, we found that a subtotal gastrectomy with an antecolic anastomosis had been done, but he did not have a loop of small bowel threaded through this as we had suspected. Why not, I do not know, because it makes a beautiful trap. Also, the jejunum had been anastomosed over the transverse colon, with a very short loop that may have accounted for some of the postoperative symptoms. We were able to thread the Miller–Abbott tube down through the anastomosis and the distal link of jejunum very nicely on the operating table, and by suction from above we slowly decompressed the small bowel. The tube obviously had gone down into the proximal blind loop of jejunum during the manipulation prior to laparotomy.

At a point approximately 40 cm. from the ileocecal valve, we encountered a large bolus of material within the lumen of the bowel back of which this obstruction had taken place. At first, we thought it probably was a mass of worms, but it turned out to be the pulp, in four sections, of an entire orange. The patient had probably swallowed these sections one after another, but they had got together in a long elliptical mass, which had stuck in this spot. Through a small incision in the bowel, we extracted this foreign body and closed the bowel. The decompression being satisfactory with the Miller–Abbott tube on the table, we were quite happy about it. If we had not been able to decompress the bowel in this manner, we should have emptied it of its contents by other means. In intestinal obstruction of this duration, the patient rarely survives the toxic effects of such material. The risk of leaving it within the bowel is very great. I have tried to locate some of Dr. George Monks's[1] original tubes on which to thread the intestines under these conditions—I once had one of these tubes in my possession and regarded it as a relic. Dr. David Cheever,[2] a few years ago, revived and used such a method. Recently, Wangensteen[3] has called attention to the value of a similar maneuver.

Aside from a brief pulmonary complication, this man did very well.

A Physician: Is it not true that foreign bodies will stop at that location?

Dr. Allen: It is the narrowest portion of the ileum and is somewhere in the neighborhood of 40 cm. from the ileocecal valve. Why there, I do not know. That is also the common site of a Meckel's diverticulum. Does Dr. Mallory know whether this has anything to do with the narrowing of the bowel in this location?

Dr. Tracy B. Mallory: No.

Dr. Allen: Anatomically, that is considered the narrowest area in the small bowel.

Clinical Diagnosis

Intestinal obstruction.

Dr. Smithwick's Diagnosis

Small-bowel obstruction due to adhesive band.

Anatomical Diagnosis

Small-bowel obstruction due to phytobezoar.

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TREATMENT OF PNEUMONIA IN THE HOME

The introduction of chemotherapy with the sulfonamide drugs has revolutionized many beliefs concerning the treatment of acute infectious diseases. Not only has the mortality from many infections been markedly reduced, but most of the laborious methods of treatment either have been rendered totally unnecessary or are now resorted to only infrequently.

The severely ill patient with pneumonia — tense, flushed, markedly dyspneic and cyanotic, enclosed in an oxygen tent and with a distended abdomen covered with poultices or stupes — was a common sight in any large medical ward throughout the pneumonia season only a few years ago. It is now rare to find such a case for demonstration to students, even in large general hospitals. This change is due in part to the fact that the diagnosis of pneumonia is being made early in the course of the disease, but particularly to the institution of chemotherapy with effective sulfonamide drugs as soon as the existence of an acute pulmonary infection is suspected.

The use of the first sulfonamide drugs — sulfanilamide and later sulfapyridine — was accompanied by severe toxic effects that necessitated great vigilance and many special diagnostic and therapeutic procedures. For this reason, and because persistent and adequate treatment with the sulfonamides is essential for the best results, most physicians believed that it was only fair to themselves and to their patients that sulfonamide therapy should be carried out in hospitals, where adequate personnel and other facilities are more readily available for the management of problems as they arise.

As physicians acquired more experience in the use of the sulfonamide drugs and as new derivatives became available that were more effective and at the same time gave fewer reactions, the attitude toward hospitalization changed materially. The physician is now in a position to administer effective therapeutic doses of such drugs as sulfathiazole and sulfadiazine in the home and to carry out the essential observations with a minimum of effort.

Elsewhere in this issue of the *Journal*, there is a report on the treatment of 132 cases of pneumonia with sulfathiazole in the home. The patients were from among the poor residents of Boston who could not afford to pay for the services of private physicians. The success of this venture is indicated by the very low mortality — 3.8 per cent — and by the rarity with which complications of either the disease or the treatment were encountered. The results are all the more remarkable since a large percentage of the patients were over fifty years old and some of them had positive blood cultures. These favorable results are due

in large measure to the early institution of treatment and to the diligence and interest of the physicians engaged in this work. Nevertheless, most of the procedures that these district physicians were called on to do could easily be carried out by any private practitioner. This excellent work has served to relieve, in some measure, the marked overcrowding of the public wards of Boston hospitals during the season when respiratory infections are prevalent.

Some degree of caution is still necessary, especially since all the newer drugs give rise to untoward reactions, particularly in the urinary tract. The practice of forcing fluids is to be stressed, particularly in patients treated with these drugs in the home, and special precautions should be taken with those who are suspected of having impaired renal function. Blood counts must be taken frequently in patients who require prolonged treatment (over periods lasting more than two weeks), to forestall the occurrence of agranulocytosis. The danger that the patient will not carry out the treatment or will discontinue it too soon is perhaps of greater consequence in the domiciliary management of severe infections like pneumonia. The success of sulfonamide treatment in this disease, as in most infections treated with these agents, depends on adequate and continuous treatment until a complete cure is effected.

The successful experiences of the Boston Dispensary physicians are not unique and are not dependent entirely on a highly trained "team." Physicians in private practice can obtain similar results. This is demonstrated in a recent report by McClure,* who reviewed 386 cases of pneumonia treated by private practitioners in Ontario. Sulfapyridine alone was used in the treatment of 92 per cent of these cases, most of which were associated with type-specific pneumococci. It is of interest that the mortality in the cases treated with sulfapyridine was 3.7 per cent, which is almost identical with that reported in the patients treated in Boston with sulfathiazole. It is also worthy of note that the average total amount of sulfapyridine used was only half as much as that of sulfathiazole. The difference may very well be related to the more frequent and severer nausea and vomiting that accompany sulfapyridine treatment and induce both patient and physician to discontinue treatment sooner than might otherwise be deemed necessary.

*McClure, W. B. Chemotherapy in pneumonia cases treated by private practitioners. *Canad. M. A. J.* 45:26-28, 1941.

A COMPLIMENT

Under the title, "*The New England Journal of Medicine*," the following editorial appeared in the April 15 issue of the *New York State Journal of Medicine*:

> In a letter to the New York *Times* of March 25, 1942, Dr. Henry R. Viets of Boston, quoting an editorial in that paper, of March 22, entitled "A Yale Genealogy," says:
>
> It would be interesting to trace the lives and usually early deaths of magazines that have taken the name of New England. . . . One stalwart in that line is the *New England Journal of Medicine*, the first journal of medicine in this country, if not in the world, which has continued, despite changes in form and of name, in uninterrupted existence since 1812. The name "New England" was held from 1812 to 1828, when the magazine became the *Boston Medical and Surgical Journal*. In 1928, the name again became *New England Journal of Medicine*.
>
> We are beholden to Dr. Viets for this interesting information about this stalwart publication. Always an appreciative admirer of the contents of the *New England Journal of Medicine*, the NEW YORK STATE JOURNAL OF MEDICINE now finds itself viewing with reverence this additional, and until now to us unknown, attribute of great age of our northerly sister. We are content to have the respectable, even genteel, name of New England carried forward from generation to generation by such a worthy vessel. The episode of the Boston wild oats, from 1828 to 1928, has already been forgiven, and will soon be forgotten. In another century, not one of us now living will remember it.
>
> In the light of this new learning from the pen of Dr. Henry Viets, historian, we shall henceforth turn the pages of our copies of the *New England Journal of Medicine* gently, with great delicacy. And as they rustle under our disturbing touch, they will remind us of the glories of her youth, the crinolines of Dolly Madison, the exploits of Commodore Perry and Captain Lawrence, and of the *Constitution* and the *Guerriere*, *Old Ironsides*, Tecumseh's Conspiracy, and Harrison at Tippecanoe.

This stalwart, "northerly sister," admitting that great age in itself is not to be taken too seriously and is often, indeed, a subject to be avoided in conversation with the truly old, appreciates

the admiration, reverence and delicate humor of the *New York State Journal of Medicine*. Perhaps, along with Captain Lawrence, Commodore Perry and Dolly Madison's crinolines, the rustling pages will evoke a memory of the dry, salubrious chuckle of Dr. Holmes.

OBITUARY

FREDERICK TAYLOR LORD

1875 - 1941

FREDERICK TAYLOR LORD was born in Bangor, Maine, on January 16, 1875. His boyhood was spent in Lexington, Massachusetts, and he prepared for college in the public schools of that town. In 1897, he obtained from Harvard his degree of bachelor of arts. His excellent reading knowledge of French and German was doubtless acquired during his college days. Only three years later, — in 1900, — he graduated from the Harvard Medical School. His first knowledge of clinical medicine must have been acquired in the Massachusetts General Hospital during his internship, for at that time there were no clinical clerkships at Harvard and fourth-year students were not allowed in the wards. From the time he entered the hospital as a house officer until he retired as a visiting physician in 1935, his life was intimately connected with the Massachusetts General Hospital.

On finishing his internship, Dr. Lord at once made a beginning in private practice, but at the same time he began research in bacteriology at the Massachusetts General Hospital under the personal direction of Dr. J. Homer Wright, who was as skilled in bacteriologic technic as he was in pathology. At the outset, he received help and inspiration from Dr. William H. Smith, who had worked some time in the laboratory when Dr. Lord was a novice. Undoubtedly Dr. Wright and Dr. Reginald H. Fitz were the two men who influenced him most. His first study published from the laboratory — his second publication — dealt with the influenza bacillus, which he cultivated from 11 cases of acute and 18 cases of chronic infection of the upper respiratory tract. This paper appeared in 1902. Additional studies of the influenza bacillus appeared in 1905. His work on influenza made such a favorable impression on Dr. Osler that he was asked not later than 1905 to prepare the section on influenza for Osler's system of medicine. In this monograph and the two subsequent ones, Dr. Lord presented a detailed analysis of the cases of influenza admitted to the Massachusetts General Hospital over a period of years. Prior to his work in bacteriology, he published an analysis of 26 cases of so-called "typhoid spine" that he collected from the literature. In its preparation, his knowledge of French and German stood him in good stead.

Diseases of the respiratory tract were always his special interest, dating from his early work with the influenza bacillus. With Dr. Walter James, he contributed the chapter "Diseases of the Pleura" to Osler's system, which was published in 1907.

This early bacteriologic work was carried out in confined quarters. Dr. Means called it a "cubbyhole." Finally, after many years, he acquired a more adequate laboratory, in which he and Dr. Robert N. Nye carried out valuable studies on the biology of the pneumococcus. Pneumonia and tuberculosis were his major subjects of study in later years. He was one of the first to investigate the antipneumococcus serums, and he did much to make serum therapy in pneumonia available to the physicians in Massachusetts through his connection with the Massachusetts Department of Public Health. In collaboration with Drs. Roderick Heffron and Elliott S. Robinson, he wrote two books on the treatment of pneumonia; the second of these dealt with chemotherapy as well as serum therapy.

In 1915, his valuable book, *Diseases of the Bronchi, Lungs and Pleura*, appeared, and ten years later a second edition, thoroughly revised and including a section on pulmonary tuberculosis. In addition to a most thorough study of the literature, this work contains a great deal of original material based on Dr. Lord's experience at the Massachusetts General Hospital and in his private practice. The most careful analysis of medical records is presented. He followed the course of patients for years after he had last seen them. For example, he wrote that of the 65 patients with bronchial asthma in his series whose subsequent courses were known, 11 were completely free from asthma for two to six years after their last visit. This statement, which occupies only three sentences of his text, represents a great deal of laborious work in record making and correspondence with former patients, a task that few physicians would undertake. The book was dedicated to the memory of Dr. Reginald H. Fitz. It is clear that his medical career was largely patterned after that of Dr. Fitz. In the writings of both are the same thorough knowledge of the literature and the same analysis of carefully recorded clinical and pathological observations. This book of outstanding value has never received the recognition it deserved. It is still one of the best treatises on diseases of the respiratory organs.

Dr. Lord was a remarkably successful teacher. Year after year, he gave a course for practitioners, consisting of one exercise a week over a period of many weeks. As many as a hundred physicians attended this course at one time.

His consulting practice for many years was one of the largest, if not the largest, in Boston. The bag filled with diagnostic equipment, which he took with him on consultations, was said to be the largest on record. He examined his patients with meticulous care and made careful records. He made good use of this abundant material. In support of this statement, the following facts are cited. In the birthday volume presented to Sir William Osler in 1919, Lord reported an analysis of 100 cases of pulmonary abscess. In 1925, only six years later, he was able to add 127 cases that he had observed and studied.

During the last seven years, his interests broadened, and problems of public health became his chief concern. He served on advisory committees of both the Boston City and the Massachusetts State departments of health.

As a man, he was kindly, serene and modest. He was charitable of the faults of others and was not given to criticism. But he could speak out fearlessly when an incompetent man was proposed for a position of responsibility. He was in the best sense of the term a self-made man. He carried on his studies and hospital work without pay and largely supported his laboratory at his own expense. He showed the manner of man he was by his work. He talked little and did much. He was a true scholar and scientist, a physician without guile and a man whose memory we cherish and honor.

J. H. P.

MEDICAL EPONYM

PAGET'S DISEASE (PRECANCEROUS ECZEMA)

This condition was described by Sir James Paget (1814–1899) in a paper, "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland," that appeared in the *St. Bartholomew's Hospital Reports* (**10**:87-89, London, 1874). A portion of the text follows:

> I believe it has not as yet been published that certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of scirrhous cancer in the mammary gland. I have seen about fifteen cases in which this has happened. . . . In all of them the disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of very acute diffuse eczema, or like that of an acute balanitis . . . in every case which I have been able to watch, cancer of the mammary gland has followed within at the most two years, and usually within one year. . . .
>
> The formation of cancer has not in any case taken place first in the diseased part of the skin. It has always been in the substance of the mammary gland, beneath or not far from the diseased skin, and always with a clear interval of apparently healthy tissue.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: RUPTURE IN TUBAL PREGNANCY CAUSING FATAL PERITONITIS

A thirty-four-year-old primipara whose past history was entirely irrelevant and whose physical examination was quite normal was seen six weeks after her last catamenia. While working about the house, she was seized with severe abdominal pain, and the physician who responded to her call took her immediately to the hospital, where a diagnosis of ectopic pregnancy was made and operation advised. The patient's husband refused permission for operation, and three days later the patient went home. Eight days after discharge, she returned to the hospital in very poor condition, with a rapid pulse and a low blood pressure. An operation was immediately performed. The abdomen was full of blood, and the contents of the left tube were removed. There were many adhesions about this tube, whose removal resulted in considerable trauma to the adherent intestine. The patient was transfused, and the abdomen was closed, a drain being left at the base of the left adnexa. For twelve days, recovery was satisfactory. At the end of this time, signs of intestinal obstruction appeared, requiring a subsequent operation. At operation, the intestines were found to be kinked and adherent, and an abscess mass was present in the region of the removed left tube. The patient was again transfused, but her condition continued to grow worse until death, which occurred ten days following the second operation.

Comment. This fatal case of a rupture in an extrauterine pregnancy was due solely to ignorance or stubbornness on the part of the patient's husband; the medical profession was in no way to blame. The diagnosis was made at the onset of the illness; operation was advised and was refused. The patient went home and returned to the hospital in very poor shape after a second hemorrhage. Had the operation been performed at the time of the first attack, simple surgery would have been sufficient. The operation for the subsequent attack with greater hemorrhage was complicated by the intestinal adhesions surrounding the ruptured tube. These were freed during the salpingectomy, and much raw surface was present that would not have resulted had the operation

been performed earlier, as the surgeon desired. At the second operation, performed because of signs of intestinal obstruction, an abscess was found at the base of the left tube; this was caused by the rupture of the intestine. The patient apparently recovered from the intestinal obstruction and died of general peritonitis.

Each year, several patients die of the complications of tubal pregnancies. Some of these deaths can be attributed to wrong diagnosis on the part of the physician, or to his inability to appreciate the necessity for laparotomy. Some cases are definitely due to ignorance on the part of the patient, who does not seek medical advice when the early signs of irregular bleeding present themselves.

COMMITTEE ON ARRANGEMENTS

PROGRAM SUBSTITUTIONS

On account of the illness of Dr. Edwin H. Place, Dr. Conrad Wesselhoeft has courteously consented to speak. His subject will be "Mumps as a Military Disease."

The Section of Obstetrics and Gynecology will meet in Perkins Hall, Women's Educational and Industrial Union, 264 Boylston Street, instead of at the Tavern Club as previously announced.

WILLIAM T. O'HALLORAN, *Chairman*

DEATHS

BREEN — JOHN J. BREEN, M.D., of Lowell, died February 3. He was in his fortieth year.

Born in Lowell, the son of the late John J. and Harriett (Greenhalge) Breen, he received his degree from St. Louis University School of Medicine in 1928. After serving his internship at St. John's Hospital, Lowell, Dr. Breen began general practice in Lowell. He was associated with the staffs of St. John's Hospital, the Lowell Visiting Nurses Association and the Lowell Day Nursery, and was a member of the Massachusetts Medical Society and the American Medical Association. At the time of his death, he was awaiting call for active service with the United States Army.

WHEELER — JOHN B. WHEELER, M.D., of Burlington, Vermont, died May 1. He was in his eighty-ninth year.

Born in Stowe, Vermont, Dr. Wheeler received his degree from Harvard Medical School in 1879. He was an intern at the Massachusetts General Hospital. From 1881 to 1924, he was associated with the surgical department of the University of Vermont College of Medicine — as instructor, clinical professor and professor. He was one of the founders of the American College of Surgeons and the New England Surgical Society. He was a fellow of the Vermont State Medical Society and the American Medical Association, and was a former member of the Massachusetts Medical Society.

Two daughters and a sister survive him.

WAR ACTIVITIES

CIVILIAN DEFENSE

CHEMICAL WARFARE COURSE

Twenty-five physicians from the First, Second and Third defense regions attended a special course, "Medical Aspects of Chemical Warfare Agents," at the University of Cincinnati College of Medicine, February 23 to 26, inclusive, under the auspices of the Medical Division of the United States Office of Civilian Defense with the cooperation of the Chemical Warfare Service of the United States Army. It is expected that the class will be repeated for physicians of other regions in the coming months.

It is intended that physicians who have taken this course will be able to set up similar units of instruction in their own localities and will teach both medical and civilian groups. The students were selected by the regional medical officers in the three eastern regions. There was no charge by the university for tuition and materials, the course being offered as a contribution to the war effort. Travel and living expenses of the students were financed locally through state and local defense councils.

NEW HAMPSHIRE MEDICAL SOCIETY

NOTE

The new head of the New Hampshire State Board of Health is Dr. Ralph E. Miller, of Hanover, assistant dean and associate professor of pathology at Dartmouth Medical School. He succeeds Dr. George C. Wilkins, of Manchester, who recently retired after having served in that capacity for many years.

DEATH

WEBBER — NORMAN B. WEBBER, M.D., of Manchester, died February 22.

Born in Thetford, Vermont, on August 15, 1875, Dr. Webber graduated from the University of Vermont College of Medicine in 1903 and had practiced medicine in Manchester since 1904. He was associated with the Notre Dame and Elliot hospitals. He was a member of the New Hampshire Medical Society and the American Medical Association.

MISCELLANY

SCHERING AWARD WINNERS

Winners of the Schering Award for 1941 have just been announced by the Association of Internes and Medical Students. Fred Feldman, '42, Albany Medical College, and Cesare Lombroso, '42, Johns Hopkins University School of Medicine, have been awarded first and second prizes, respectively, by the Committee of Judges, a group of outstanding American investigators. Elizabeth Brown, Albany Medical College, and Clarence Denton, Long Island College of Medicine, have been awarded third prize. The subject for the 1941 competition was "The History of Endocrine Research."

The Schering Award, established by the Schering Corporation and conducted by the Association of Internes and Medical Students, offers two tuition scholarships of a year and a half year, respectively, to be granted for the best papers dealing with some aspect of endocrinology submitted by undergraduate medical-school students in the United

States or Canada. In all, papers were submitted by students representing twenty-four medical schools, an indication of the wide interest and response occasioned by the competition.

Plans for the Schering Award competition for 1942, which will again be sponsored by the Association of Internes and Medical Students, are being formulated. The subject for this year's paper, as well as the full panel of judges, will be announced shortly.

ANNUAL PRIZE SUBSCRIPTION

The annual prize subscription offered by the *New England Journal of Medicine* for the best undergraduate contribution to the *Tufts Medical Journal* has been awarded to Mathew Ross, '42, for his paper "Acute Appendicitis of Childhood and Its Differential Diagnosis," which appeared in the March, 1942, issue. The paper "Constitutional Medicine," by D. A. Freedman, '43, received honorable mention; it appeared in the November, 1941, issue of the journal.

NOTES

At the recent meeting of the American Heart Association in New York City, Dr. Paul D. White, of Boston, was elected president for the ensuing year.

Two important appointments to the staff of the Harvard Medical School, effective July 1, were recently announced by the University. Dr. Rene Jules Dubos has been appointed George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine, to succeed Dr. Ernest E. Tyzzer, who becomes professor emeritus. Dr. George W. Thorn has been appointed Hersey Professor of the Theory and Practice of Physic and Physician-in-Chief of the Peter Bent Brigham Hospital, to succeed the late Dr. Soma Weiss.

REPORT OF MEETING

NEW ENGLAND PEDIATRIC SOCIETY

A regular meeting of the New England Pediatric Society, held at Longwood Towers on January 14, was presided over by Dr. R. Cannon Eley. An obituary of the late Dr. Kenneth Blackfan was read. The speaker of the evening was Dr. Joseph W. Ferrebee, of the new Harvard School of Dental Medicine, who discussed the dental problem as related to the practice of pediatrics.

At present, the cost of dental care is equal to or even greater than that for medical treatment. Twenty per cent of those examined by the military authorities in the present selective-service group are found to have reason for rejection in the condition of their teeth. The repair of teeth, which accounts for two thirds of the dentists' work, is much more costly than prophylactic treatment. Furthermore, this need will become more urgent with the natural regression of the teeth attendant on our civilized habits of eating and preparing foods. It is well known that milling removes 90 per cent of certain vitamins, for example.

The problem for the pediatrician springs partly from the fact that the calcification of the primary dentition takes place from midterm on, whereas secondary calcification occurs from term through early childhood. Contrary to popular belief, primary dentition is not unimportant, for at that time normal chewing habits begin that result in proper spacing of the teeth and development of the jaw. And proper spacing of the teeth prevents the dirt and pyorrhea that accompany faulty cleaning. Furthermore, caries may be spontaneously walled off in a few weeks by secondary dentine if the person is placed on good general home care and proper diet.

At present, the maximum incidence of visits to the dentist occurs in the age group from fifteen to twenty-one years, whereas the minimum is in those from three to eleven years. For better results, these should be reversed, so that proper prophylaxis might be carried out. The essential factors in prevention of later dental troubles are proper home care of the teeth, an adequate diet and frequent visits to the dentist at an early age.

BOOK REVIEWS

Lectures on War Neuroses. By T. A. Ross, M.D. 12°, cloth, 116 pp. Baltimore: Williams and Wilkins Company, 1941. $2.00.

This brief volume is a valuable addition to the subject of war neuroses. It was written by a physician who had a large experience in World War I and subsequently continued to be interested in civilian neuroses in his practice of medicine. He has been in touch with the subject in World War II, and he gives some brief notes on the experiences of the English soldier escaping from Dunkirk and the effect of bombing on the public.

The volume is divided into only four chapters: one presents a preliminary discussion of neuroses in general; the second deals with the acute war neuroses; and the third and fourth discuss the more chronic conditions. The material in these chapters has been given as lectures at medical centers in the last twelve months.

Full of sound common sense and written by a man who is completely familiar with his material, this little book is an outstanding contribution to the subject. It is, moreover, timely, and should be put in the hands of every medical officer in charge of soldiers, sailors or civilians likely to suffer from neuroses incident to modern warfare.

Outline of Industrial Medical Practice. By Howard E. Collier, M.D. (Edin.), Ch.B. 8°, cloth, 440 pp. Baltimore: Williams and Wilkins Company, 1941. $5.00.

Out of the kaleidoscopic development of manufacturing processes during the past two decades, industrial medicine has emerged as a new field in which the general practitioner finds few landmarks or familiar paths. It is especially to orient the run-of-the-mine physician in the problems of modern industrial medicine and to furnish the plant physician with a working guide to administrative practice that this book has been prepared.

In addition to providing an exceptionally concise and practical handbook on all phases of occupational hygiene, this work is unique in emphasizing the importance of group illness in industrial medicine. Since occupational disease is something more than the aggregate of the illnesses of the individuals in the group, the plant physician, as well as the health officer, must learn to think in terms of possible common causes of group illness. The section on industrial psychology is the clearest and most constructive discussion that the reviewer has seen of that vexed but significant field.

The bibliography is well chosen for the physician who may wish to look farther into some of the sources of industrial medicine.

(Notices on page xi)